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MAY 1959

DISEASES of the CHEST

OFFICIAL PUBLICATION

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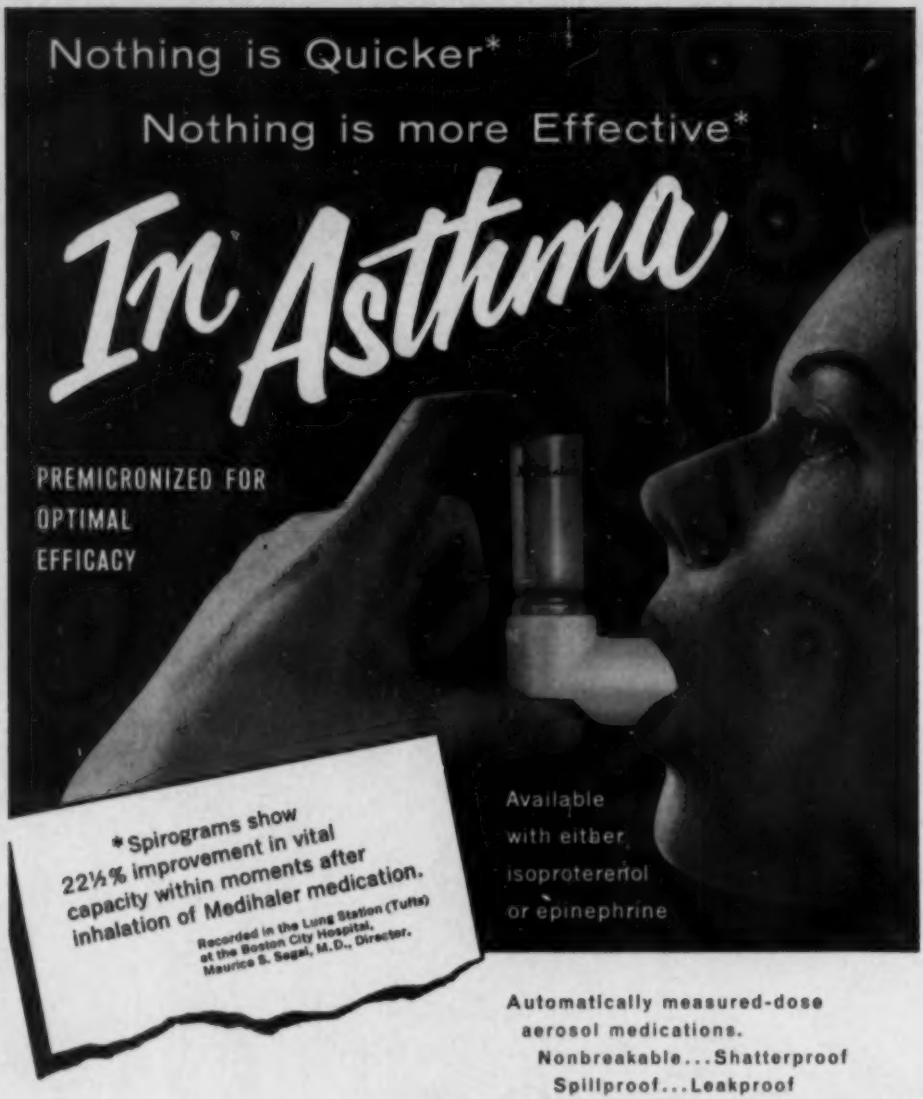
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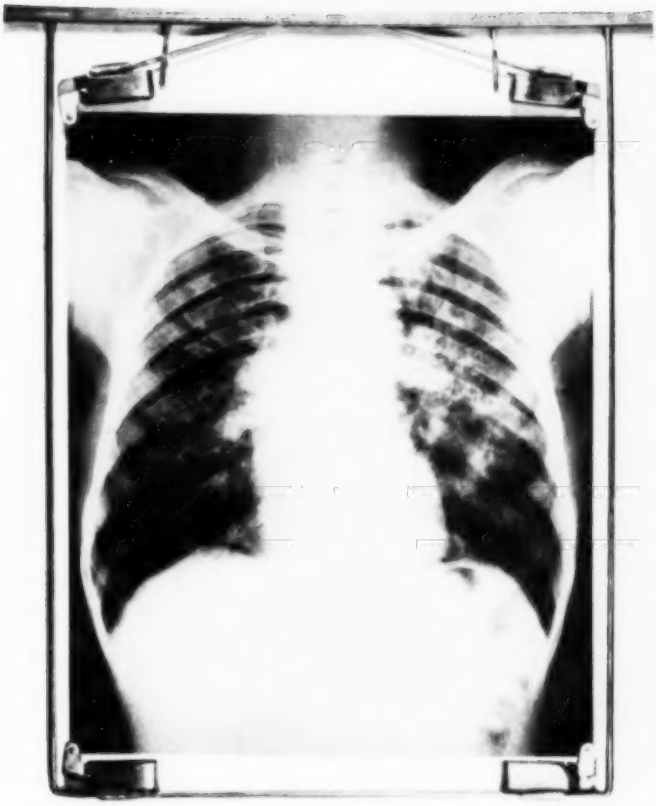

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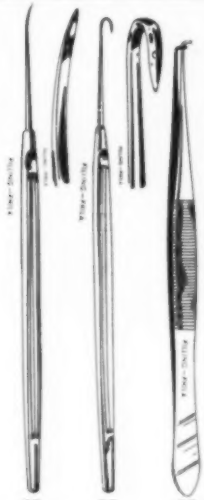

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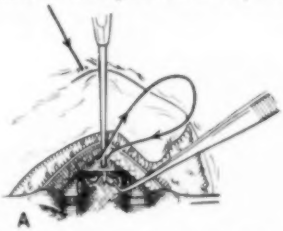

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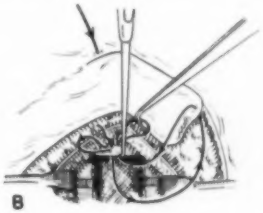

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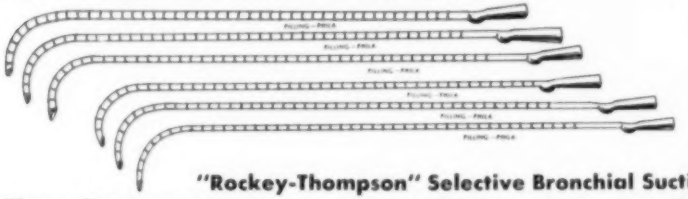

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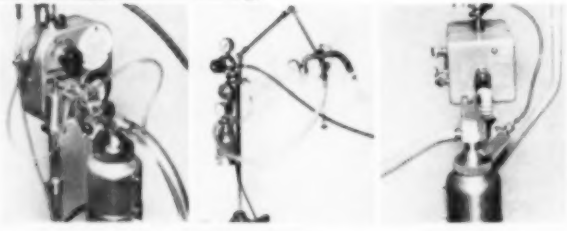

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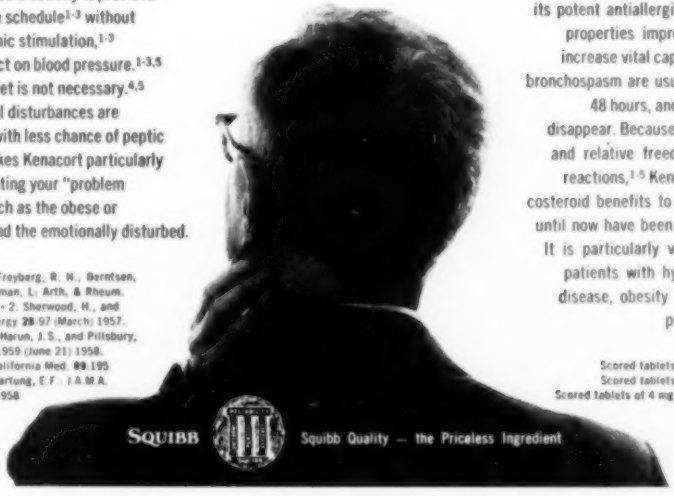

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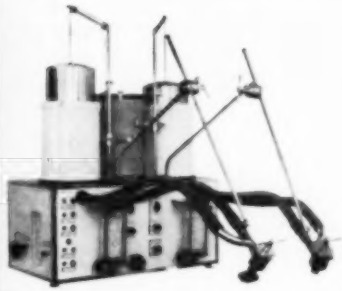

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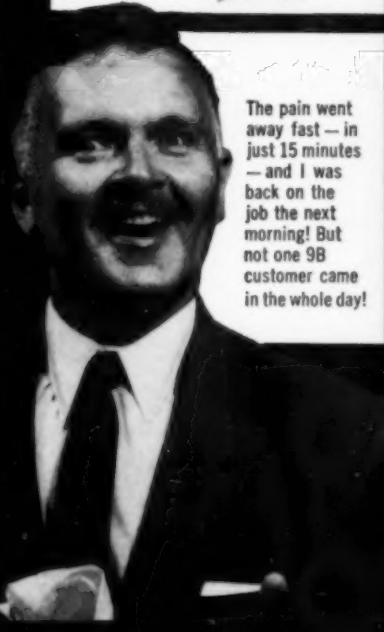

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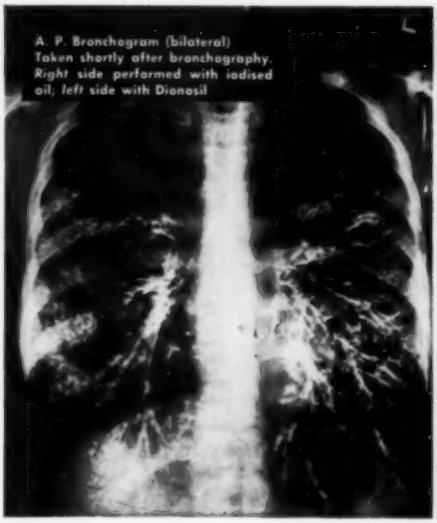

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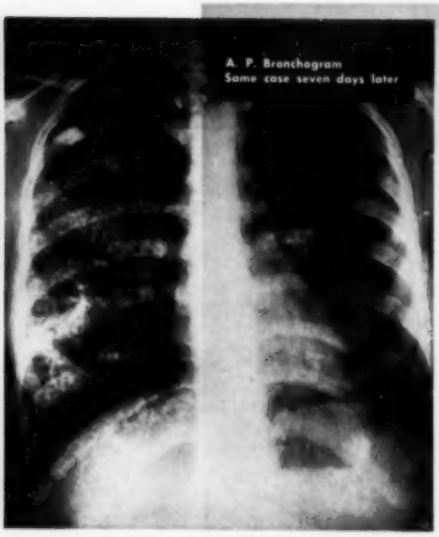

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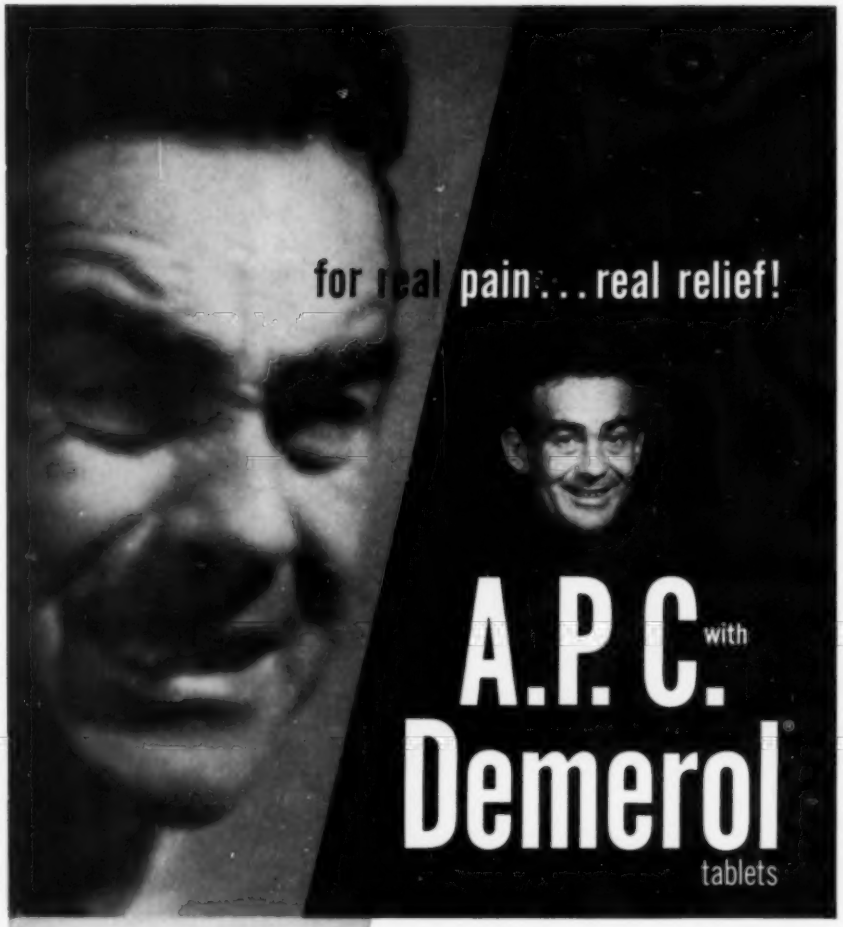

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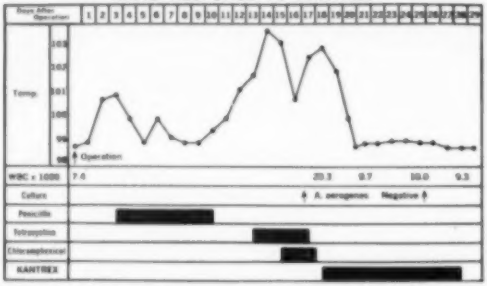

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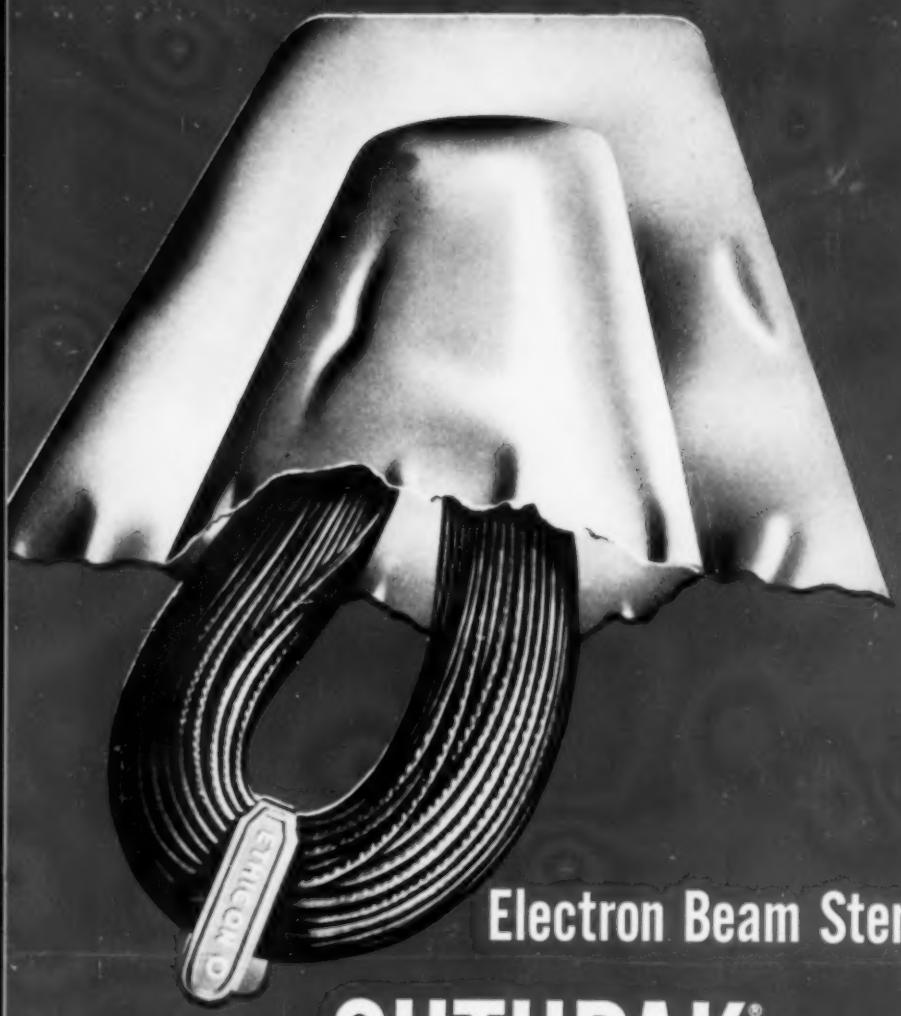

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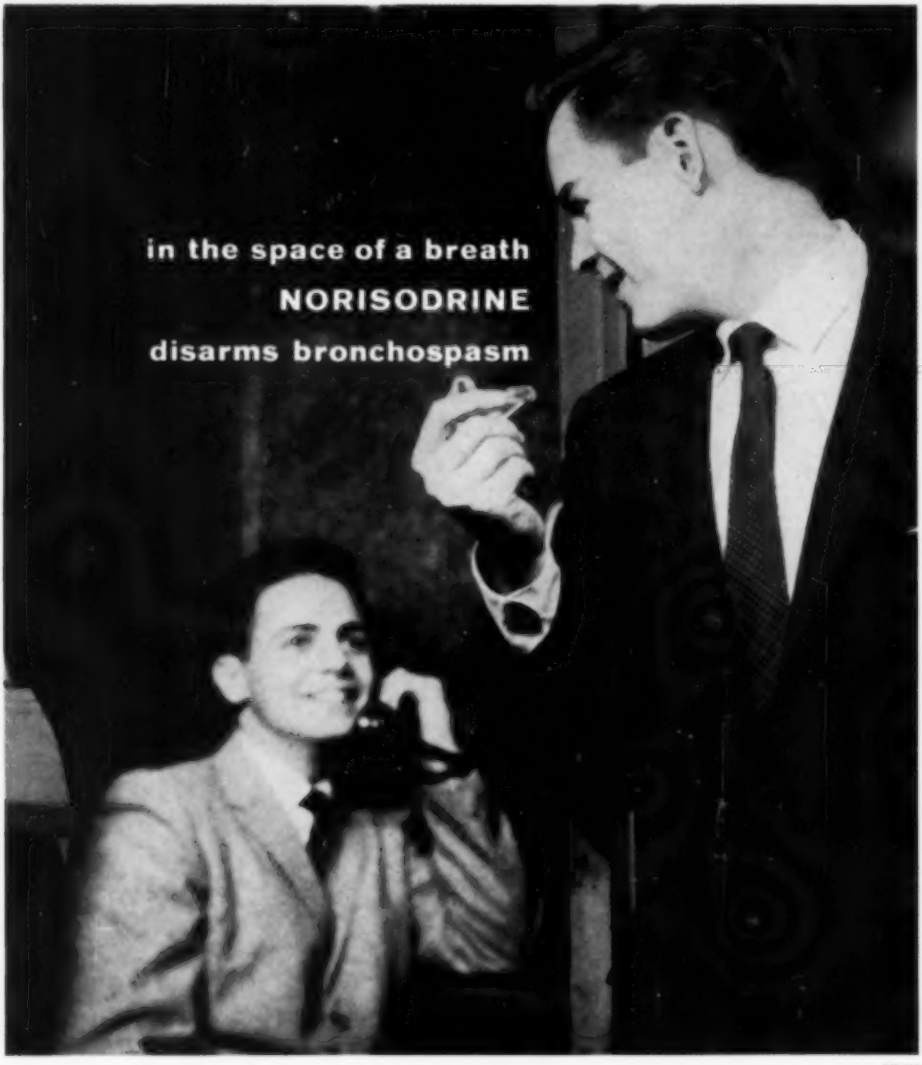

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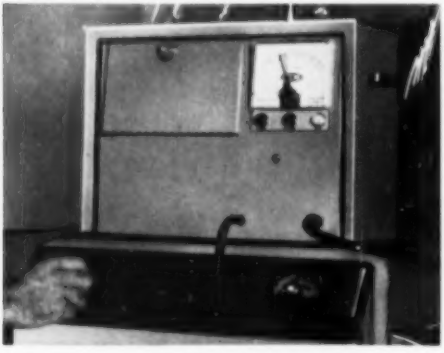

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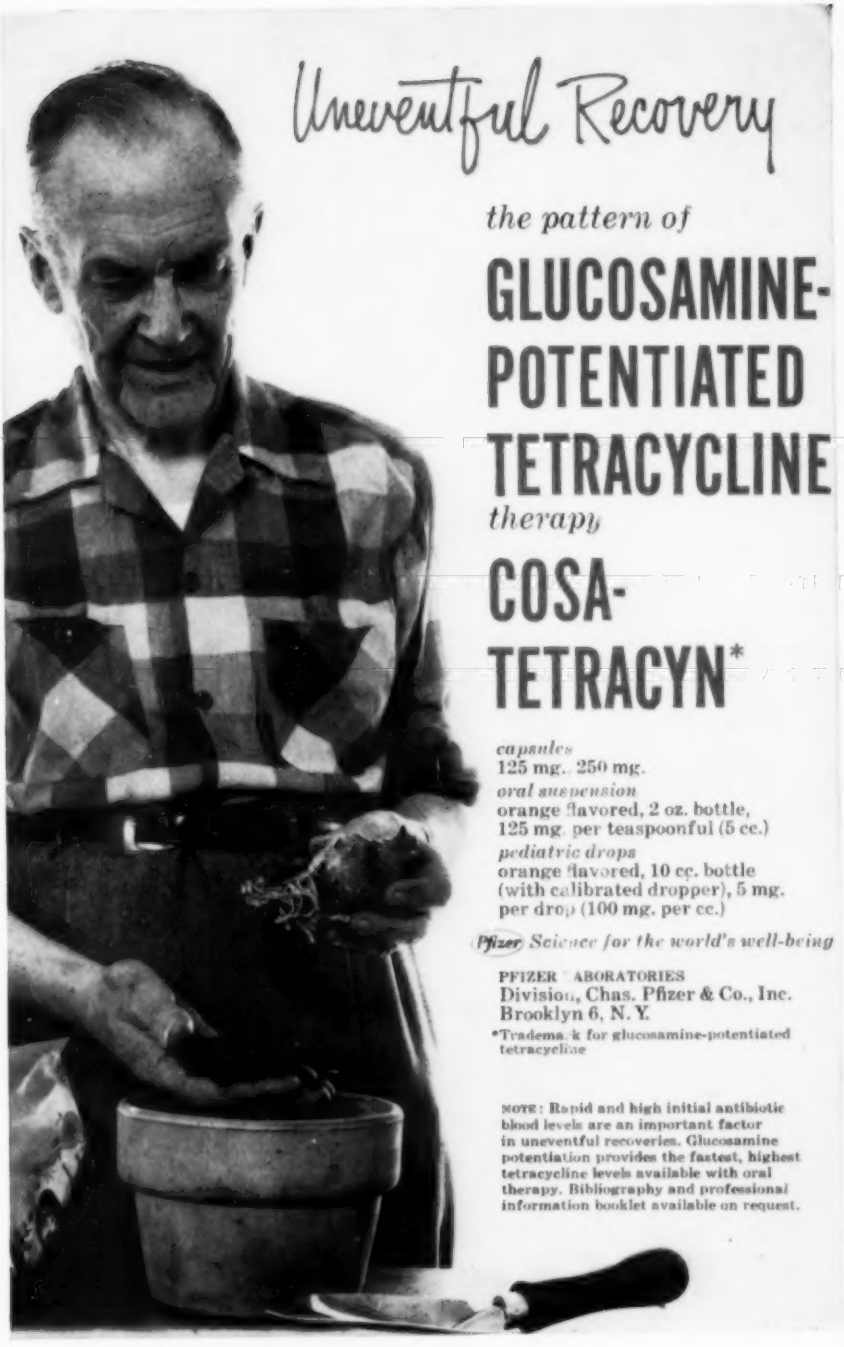

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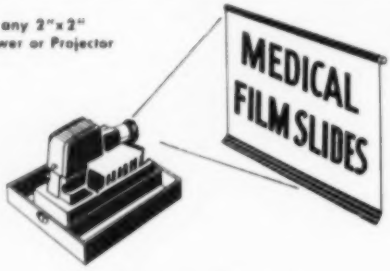

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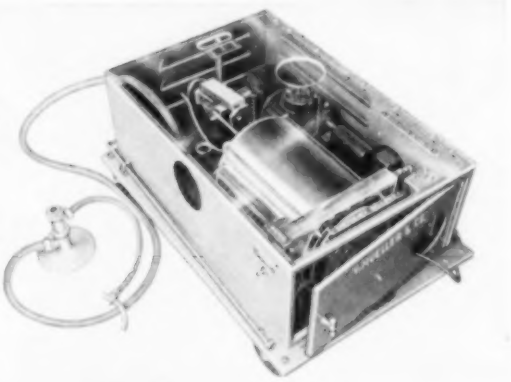

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1. Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology 8:504, Dec. 1957.
2. Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.
3. Eskwith, I. S.: The holistic approach to angina pectoris. Am. Heart J. 55:621, April 1958.

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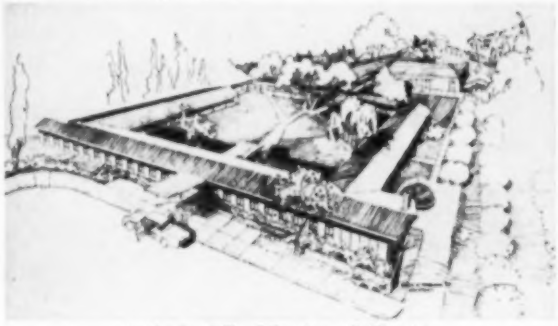

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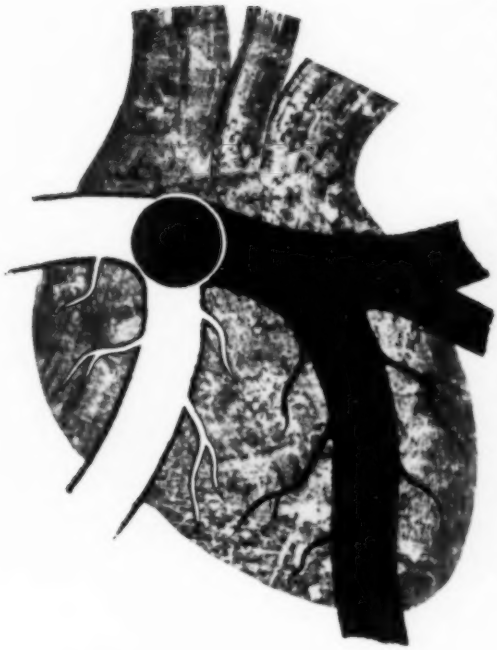

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—*Early Management of Myocardial Infarction*: B. E. Pollock; Journal of the American Medical Association, 161:404 (June) 1956.

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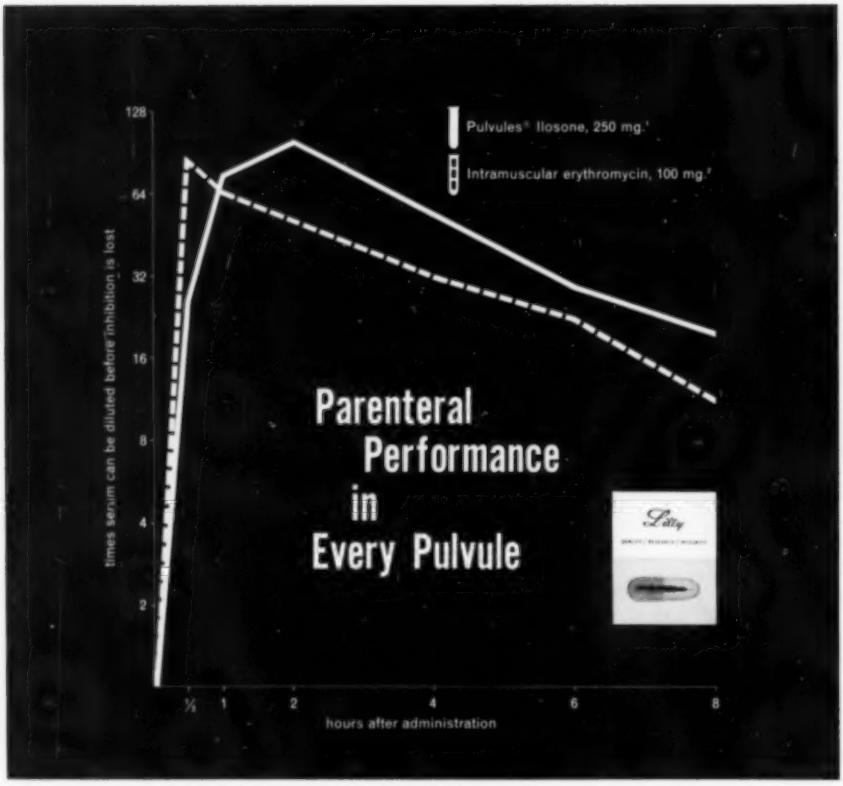

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1. Antibiotic Med. & Clin. Therapy, 5:609, 1958.

2. Data from Antibiotics Annual, p. 269, 1954-1955.

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DISEASES of the CHEST

VOLUME XXXV MAY, 1959 NUMBER 5

Studies on the Role of Intermittent Inspiratory Positive Pressure Oxygen Breathing (IPPB/I-O_2) in the Treatment of Pulmonary Edema*

WILLIAM F. MILLER, M.D., F.C.C.P.** and BRIAN J. SPROULE, M.D.†
Dallas, Texas

Pulmonary edema is a state of the lungs characterized by filling of the alveolar and many of the bronchial spaces with serous or sero-sanguinous fluid owing to a variety of conditions, Table I. These conditions must precipitate one or more of the following functional disturbances:

1. Increased pulmonary transcapillary pressure gradient.
   A. Increased pulmonary capillary pressure.
   B. Increased negative intrapulmonary pressure.
2. Decreased lymphatic reabsorption of pulmonary fluid.
3. Increased pulmonary capillary permeability.
4. Decreased colloid osmotic pressure of the blood.

An excellent review of the current concepts of the pathogenesis of pulmonary edema has been published by Luisada.[1] Even though much has been learned, our knowledge of the mechanisms is still incomplete. Certainly in most instances multiple factors must be involved.

Regardless of the etiology, once the condition exists, the patient is ill in direct proportion to the magnitude of these physiological alterations. Dyspnea of a profound degree is almost invariably present, accompanied usually by hypoxia and at times by fever and shock.

This condition often presents itself with an air of great urgency so that immediate specific therapy based on knowledge of the pathogenesis of the attack would seem most appropriate. The treatment, unfortunately, often consists of invoking enthusiastically some routine based largely on personal preference, and arising out of often dangerously misleading clinical impressions. On the other hand, therapeutic pessimism such as portrayed by some[2] is hardly justifiable.

It is not the purpose of this report to review or evaluate the numerous therapeutic agents or procedures which have been suggested, but to demonstrate and discuss the physiological basis for the use of oxygen administered

Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.
This study was supported by funds from the American Heart Association and the Dallas Heart Association.
*From the Cardiopulmonary Laboratory, Department of Internal Medicine, University of Texas Southwestern Medical School, and Parkland Memorial Hospital.
**Associate Professor of Medicine, University of Texas Southwestern Medical School.
†Research Fellow, University of Texas Southwestern Medical School.

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by intermittent positive pressure, inspiratory (IPPB/I) in the treatment of pulmonary edema. During the past four years, over 350 patients with pulmonary edema have been treated with IPPB/I-O_2 on the wards of Parkland Memorial Hospital with usually remarkable and often dramatic results.

Physiological Methods

Gas exchange studies were performed with the patients breathing ambient air (if tolerated), 100 per cent oxygen, and 100 per cent oxygen administered by IPPB/I in a random sequence. Simultaneous arterial blood and expired air samples were obtained. Analysis of expired O_2 and CO_2 was performed with the Beckman E-2 oxygen analyzer and the Liston model 16 infra-red CO_2 analyzer, both of which were checked frequently by the Scholander micro-gas analyzer. Alveolar pO_2 was calculated by the alveolar equation. Arterial blood was analyzed for O_2 and CO_2 content by the Van Slyke manometric method, while the pH was measured by the Cambridge Research meter or the Beckman GS meter, in either case with the cell at 37°C. Direct arterial O_2 tensions were measured by a polarographic method[3,5] employing the Clark electrode.[6]

Results

The 35 patients studied represent a variety of subjects with severe pulmonary edema of different etiologies. Eight of these cases are illustrative of the material and the results of the studies on them will be presented here.

Case 1: A 22 year old Negro alcoholic was admitted with a one-day history of acute gastrointestinal bleeding antedated by six months of failing health characterized by fatigability, subjective fever, weight loss, and moderate cough productive of mucopurulent sputum. A chest roentgenogram made two months prior to admission revealed right upper lobe disease, probably pulmonary tuberculosis, but he refused treatment. Physical examination revealed an acutely and chronically ill young man; not dyspneic. His blood pressure was not obtainable, temperature 98, respirations 30. The lungs revealed bronchial breathing over the right upper lobe. The chest roentgenogram showed a pneumonic process of the right upper lobe and diffuse nodular infiltration throughout the left upper lobe. Massive GI bleeding continued. In spite of transfusions totalling 3,500 cc., the hemoglobin never rose above 7 gm. and he remained either markedly hypotensive or in shock. Eighteen hours after admission, his condition being somewhat improved, he underwent general inhalational anesthesia and subtotal gastrectomy was performed. During the first two post-operative days, his blood pressure was stabilized with the aid of pressor amines and blood transfusions. During this period, he continued to be moderately hyperpneic with mild dyspnea and anoxia was suspected. Forty per cent oxygen was being administered part of this period. However, on the third post-operative day, he became severely dyspneic, began producing bloody, frothy sputum, exhibited marked neck vein distension, and shortly thereafter the blood pressure, which had been 110/70, dropped to 60/40. Auscultation

TABLE I
CONDITIONS KNOWN TO PRODUCE PULMONARY EDEMA

Left ventricular failure	Thyroid crises
Mitral stenosis	Shock
Primary renal insufficiency with azotemia	Inspiratory airway obstruction
Brain damage	Hypersensitivity reaction
Toxemia of pregnancy	Acute blood loss followed by fluid overload
Pulmonary embolism	Toxic drug or chemical reaction
Pulmonary infection	Peripheral and local neurohumoral reflex disturbances
Pulmonary inflammation, non-infectious	Severe burns
Anoxia	Beri-Beri

revealed both fine and coarse bubbling rales throughout the chest. Oxygen, 100 per cent, was given by mask for a short time but this did not relieve the hyperpnea, so, at this point, the physiological evaluation shown in Table II was performed. Following the studies, he was continued on IPPB/I* with 100 per cent oxygen and it was found that 22 cm. of water pressure satisfactorily decreased his respiratory rate and relieved dyspnea. This was continued for four hours until striking improvement had been achieved. Then high concentrations of oxygen without pressure were used. However, it became necessary to reinstitute IPPB/I** for periods of one-half hour at a time every two hours to control dyspnea. After two days on this intermittent program, dyspnea was markedly improved and the physical findings of pulmonary edema gradually cleared over the next several days. He was then transferred to a tuberculosis hospital for treatment of bilateral upper lobe disease which had, in the meantime, been confirmed as active pulmonary tuberculosis.

This is an example of pulmonary edema following severe hemorrhage and rapid blood replacement but it is possible that the presence of pulmonary infection and long-standing shock following blood loss also played important roles in the pathogenesis. The physiological studies summarized in Table II revealed the presence of marked oxygen desaturation with a large alveolar air to arterial blood pO_2 difference. Alveolar ventilation is normal as indicated by a $PaCO_2$ of 36 mm. Hg. Total minute ventilation was large but the respiratory rate was 70 per minute. After 100 per cent oxygen, although the saturation had risen to 99 per cent and ventilation had dropped, dyspnea was still not relieved and he was breathing

*The IPPB/I apparatuses used for these studies were generously supplied by V. Ray Bennett and Associates, Los Angeles, California, and the Duncan Oxygen Therapy Company, Duncan, Oklahoma.

**In each instance where IPPB/I-O_2 is used for short periods of time, a bronchodilator aerosol with a surface active agent was employed, except during studies when water only was employed.

TABLE II
GAS EXCHANGE STUDIES IN PATIENT WITH PULMONARY EDEMA

Arterial Blood	Room Air*	100% O_2 40 Minutes	IPPB-O_2† 15 Minutes	IPPB-O_2† 30 Minutes	100% O_2 20 Minutes
O_2 Saturation (per cent)	60	99	100	100	100
pO_2 (mm. Hg.)	36	124	188	275	140
pCO_2 (mm. Hg.)	36	38	28	29	....
pH	7.42	7.42	7.52	7.51	....
Alveolar pO_2 (mm. Hg.)	108	664	674	674	....
A-a pO_2 difference (mm. Hg.)	72	540	486	399	....
Ventilation (Liters/min.)	32.4	17.8	22.8	22.0	20.3
Respiratory rate	70	40	31	22	36
Tidal volume (ml.) (BTPS)	459	445	719	998	563
CO_2 production (ml.) (STPD)	401	261	137	109	208
O_2 consumption (ml.) (STPD)	469	349	320	309	330
Blood pressure (mm. Hg.) (systolic/diastolic)	60/40	65/40	80/50	95/60	90/50

*On room air breathing for only a few minutes owing to profound distress and severe hypoxia produced.

†At no time during this or subsequent studies was anything but water aerosol used.

at the rate of 40 per minute. Arterial pO_2 had risen but a large A-a pO_2 gradient still remained. He was then placed on 100 per cent oxygen by IPPB/I and the most striking change was the almost immediate decrease in the work of breathing with a reduction in the respiratory rate and a rise in arterial blood pressure. The A-a pO_2 gradient still remained large, although markedly reduced over that apparent on unassisted 100 per cent oxygen breathing, indicating a diminution in the amount of veno-arterial admixture. After one-half hour of IPPB/I, the amount of veno-arterial admixture had decreased further. This was accompanied by a further decrease in the respiratory rate and a further increase in blood pressure to 95/60. Some regression in the improvement was noted upon the withdrawal of IPPB/I with the continuation of 100 per cent oxygen unassisted, manifested principally by a rise in the respiratory rate and a decrease of arterial pO_2.

Case 2: A 44 year old Negress with known disseminated lupus erythematosus and hypertensive cardiovascular disease was admitted to the hospital with severe dyspnea of several hours' duration. During the preceding 10 months, she had been hospitalized on several occasions for similar episodes, each characterized by fever, profound dyspnea, substernal chest pain, and the production of bloody, frothy sputum. Each time she had responded to the administration of antibiotics, parenteral hydrocortisone, low salt diet, and oxygen administered by IPPB/I. She was being maintained on digitalis. Physical examination revealed blood pressure 200/110, temperature 101° F., pulse 120, respirations 40 per minute. She was gravely ill, profoundly dyspneic, was producing bloody, frothy sputum, and her neck veins were greatly distended. The heart was markedly enlarged; there was a gallop rhythm but no murmur. The lungs were filled with bubbling rales and expiratory rhonchi. She was immediately started on oxygen at the highest concentration available (approximately 85 per cent); additional digitalis was administered. Intravenous aminophylline, corticosteroids and the hypotensive agent, Arfonad, were administered by slow intravenous drip. Improvement was only slight and the dyspnea continued to be profound. At this time the physiological studies shown in Table III were obtained. Subsequently, she was maintained on IPPB/I with 100 per cent oxygen for the remaining 17 days of her life. Pressures utilized varied, but generally had to be increased gradually from 25 cm. H_2O to 45 cm. H_2O to relieve dyspnea. She could be kept comfortable by this method, but upon withdrawal

TABLE III
GAS EXCHANGE STUDIES IN PATIENT WITH PULMONARY EDEMA

Arterial Blood	Room Air*	100% O_2, 60 Minutes	IPPB-O_2, 15 Minutes	IPPB-O_2, 45 Minutes	100% O_2, 20 Minutes
O_2 Saturation (per cent)	31	86	95	100	95
pO_2 (mm. Hg.)	20	57	89	212	91
pCO_2 (mm. Hg.)	56	45	48	40	41
pH	7.28	7.39	7.34	7.41	7.37
Alveolar pO_2 (mm. Hg.)	95	662	660	668	665
A-a pO_2 difference (mm. Hg.)	75	605	571	457	574
Ventilation (liters/min.)	7.7	14.6	....	22.6	15.2
Respiratory rate	40	35	29	24	32
Tidal volume (ml.) (BTPS)	193	420	....	920	476
CO_2 production (ml.) (STPD)	129	242	....	200	220
O_2 consumption (ml.) (STPD)	154	251	....	340	275

*On room air breathing for only a few minutes owing to severe asphyxia.

of assistance, dyspnea became severe within a matter of 5 to 10 minutes and she would become confused and irrational. Seventy per cent alcohol was administered by nebulization as an anti-foaming agent, and although there appeared to be some transient improvement, this was subsequently discontinued with no significant change.

This case is an example of severe progressive pulmonary edema arising from multiple etiologies, principally hypertensive cardiovascular disease and lupus erythematosus. On room air breathing, this patient's arterial oxygen saturation dropped precipitously to 31 per cent while the pCO_2 decreased to 20 mm. Hg., and the arterial pressure dropped from 200/110 to 100/80 within five minutes following prior, prolonged administration of IPPB-O_2. There was a marked improvement in oxygen saturation after 100 per cent oxygen breathing for 60 minutes. The respiratory rate decreased and total ventilation increased, indicating a slower, deeper, and more effective ventilatory pattern. However, after 15 minutes of IPPB-O_2, the arterial oxygen saturation improved to nearly normal, but there still remained a large A-a pO_2 gradient, indicating a high degree of veno-arterial admixture. After 45 minutes of IPPB-O_2, the gradient diminished significantly but still remained high. By this time, the respiratory rate had decreased to 24/minute and respiratory distress was almost completely relieved. In order to ascertain the permanency of these changes, the patient was placed back on 100 per cent oxygen by mask without IPPB, and regression in all functions occurred within 20 minutes. The increasingly high pressures subsequently utilized in this case indicated the progressive change that was occurring in her pulmonary system, resulting in increased stiffness or decreased compliance of the lung requiring progressively higher respiratory pressures in order to relieve the increasing work of breathing.

Case 3: This 57 year old colored woman, a known diabetic, with Kimmelstiel-Wilson syndrome, hypertensive and arteriosclerotic heart disease with a previous history of myocardial infarction, was readmitted with a two-week history of increasing edema, orthopnea, and exertional dyspnea. The day of admission, her respiratory distress became quite severe and was accompanied by coughing, wheezing and rattling. The blood

TABLE IV
GAS EXCHANGE STUDIES IN PATIENT WITH PULMONARY EDEMA

Arterial Blood	Room Air	100% O_2 40 Min.	IPPB-O_2 30 Min. 25 Cm. H_2O
O_2 saturation (per cent)	81	100	100
pO_2 (mm. Hg.)	58	357	560
pCO_2 (mm. Hg.)	36	37	35
pH	7.45	7.43	7.46
Alveolar pO_2 (mm. Hg.)	110	657	670
A-a pO_2 difference (mm. Hg.)	42	300	110
Ventilation (liters/min.)	6.6	6.6	8.4
Respiratory rate	26	22	20
Tidal volume (ml.) (BTPS)	243	300	420
CO_2 production (ml.) (STPD)	142	120	130
O_2 consumption (ml.) (STPD)	200	164	170
Mean arterial pressure (mm. Hg.)	120	170	180
Mean venous pressure (mm. Hg.)	32	24	18

pressure was 210/120, pulse 100, respirations 32, temperature 99° F. There was marked pitting edema up to the level of the clavicles. The neck veins were distended. There were marked retinovascular changes with micro-aneurysm formation. The chest revealed marked intercostal retraction on inspiration and diffuse, intense musical rhonchi and rales. The heart was markedly enlarged and there was gallop rhythm but no murmurs. The liver was markedly engorged, tender, and palpable 6 cm. below the right costal margin. At the time of her arrival at the hospital, she was referred to the laboratory for study. Physiological data shown in Table IV were obtained. Following this, she was maintained on almost continuous assistance by IPPB/I with 100 per cent oxygen for about 48 hours. Marked diuresis with weight loss of 22 pounds resulted. There was marked improvement in her symptoms although she was still mildly dyspneic at rest. At this point, oxygen by mask was utilized with intermittent periods of IPPB/I one hour out of three, and over the next week, respiratory assistance was gradually decreased and finally discontinued when respiratory distress ceased. By this time she had lost 35 pounds of edema fluid and the lungs were entirely clear.

This is an example of moderately severe pulmonary edema in a patient with heart disease of multiple etiologies in whom the response to treatment was slow by virtue of the magnitude of the long-standing failure with marked over-expansion of the extracellular space. Permanent relief from the respiratory distress could not be achieved until after diuresis, effected by digitalis, bed rest, low salt diet, and mercurial diuretics in addition to oxygen therapy.

Case 4: A 40 year old white oil well surveyor five days prior to admission had received a 12,000 volt electrical shock which caused his clothing to catch fire, resulting in a 48 per cent body surface burn of second and third degree type. He received emergency treatment at an outlying hospital and, when his condition began to deteriorate, as evidenced by diminished urinary output and progressive respiratory distress, he was transferred via an airplane, with a non-pressurized cabin but under oxygen, to Parkland Memorial Hospital. At the time of admission, he was semicomatose with severe respiratory distress characterized by inspiratory retraction of intercostal spaces and expiratory grunting. Diffuse, sibilant and medium moist rales were heard throughout the lungs. There was marked neck vein distention during expiration with incomplete emptying during inspiration. There were occasional loud, coarse rhonchi over the upper airway with intermittent crowing respiration indicative of upper airway obstruction. Tracheostomy was performed with slight improvement in respiratory distress. Blood pressure was 70/40, pulse 100, respirations 40 per minute; the heart

TABLE V
GAS EXCHANGE STUDIES IN PATIENT WITH PULMONARY EDEMA

Arterial Blood		100% O_2 40 Minutes	IPPB-O_2 15 Minutes 25 Cm. H_2O	IPPB-O_2 45 Minutes 25 Cm. H_2O	IPPB-O_2 30 Minutes 45 Cm. H_2O
O_2 saturation (per cent)	50	75	82	82	92
pO_2 (mm. Hg.)	30	50	60	62	80
pCO_2 (mm. Hg.)	26	30	25	26	24
pH	7.10	7.11	7.17	7.20	7.22
Alveolar pO_2 (mm. Hg.)	115	670	690	690	695
A-a pO_2 difference (mm. Hg.)	85	620	630	628	615
Ventilation (liters/min.)	18.2	17.5	24.4	25.8	33
Respiratory rate	60	55	32	32	30
Tidal volume (ml.) (BTPS)	300	318	762	805	1,100
CO_2 production (ml.) (STPD)	250	262	289	290	300
O_2 consumption (ml.) (STPD)	264	276	320	325	340
Arterial Pressure (mm. Hg.)	50/20	60/40	85/50	90/60	90/60

was not enlarged. The abdomen was distended with gas, and catheterization of the urinary bladder resulted in the delivery of 250 cc. of urine. Following tracheostomy, the studies shown in Table V were performed. Subsequently, he was maintained on IPPB/I with 100 per cent oxygen humidified through a heated mainstream nebulizer in order to prevent drying of the serous and sero-sanguinous fluid that was filling the trachea. Shortly after the institution of IPPB/I with oxygen, the blood pressure rose to 90/60 and from that point on varied between 100/70 and 90/60. Because of the profound dyspnea it was necessary to maintain him on continuous assisted respiration at pressure levels ranging most of the time between 40 and 45 cm. H_2O. Even this was not adequate to achieve full saturation of the arterial blood as noted in Table V. Over the next 12 hours, he appeared to improve considerably with maintenance of the blood pressure and good urinary output. However, after that time his condition deteriorated in spite of all therapy. It was obivous that he was suffering from an overwhelming sepsis as well as an overwhelming hemorrhagic edema of the lungs, and he expired suddenly two days after admission.

This is an example of severe pulmonary edema following extensive body burn and sepsis. Post-mortem examination confirmed the clinical impression of diffuse bronchopneumonia and profound hemorrhagic pulmonary edema. The combined weight of the right and left lungs was 4,680 gm. and they sank in water. He was known to have suffered profound hypoxia, probably for several days, prior to admission, and this was felt to have played a major role in the irreversible changes. It is important to note that his respiratory function improved with increasing pressures up to the maximal pressure attainable with the assistor being used. These pressures had no adverse effect on the peripheral blood pressure and, in fact, the blood pressure rose.

In order to illustrate further the role of IPPB/I-O_2 in the treatment of pulmonary edema with shock, four additional cases studied by ear oximetry are summarized in Table VI. In each instance, hypotension or shock was present and not corrected until after IPPB/I-O_2 was administered. In case A. J., each time IPPB was stopped and 100 per cent O_2 without pressure was administered, pulmonary edema and shock would reappear. In no instance was the hypotension or shock worsened by IPPB/I.

Discussion

The nature of the anoxic disturbance in pulmonary edema has often been referred to as a diffusion defect. Moreover, although the effect of the frothy fluid in obstructing the airways has often been mentioned,[7, 8] its

TABLE VI

Patient	Diagnoses	Room Air	100% O_2	IPPB-O_2	Pressure cm H_2O
A. J.	Myocardial infarction, pulmonary edema, shock	65	80	100	15-20
N. L.	Myocardial infarction pulmonary edema, shock	76	87	99	15-20
R. H.	Hypertensive cardio-vascular disease, pulmonary edema, hypotension	74	85	100	25-30
C. S.	Poliomyelitis, pulmonary infarction, pulmonary edema, tank respirator, shock	60	75	97	20-35

role in producing anoxia was not adequately appreciated. Williams[9] has presented evidence to demonstrate that the anoxic defect in pulmonary edema is largely a result of a distribution defect rather than a diffusion gradient. The present studies showing major evidence of veno-arterial admixture with large alveolar-arterial oxygen gradients on 100 per cent O_2 breathing confirm this concept. This change indicates that some pulmonary artery blood is traversing the lung through non-ventilated areas or perhaps through shunts[10] that become operative under the circumstances of severe pulmonary disturbances.

The presence of obstructing, frothy, viscid fluid in the bronchial tree provides the basis for the use of surface active agents which reduce foaming.[11-14] This tends to reduce the obstructing effect and makes possible more effective distribution of inspired oxygen.

Often a far more important effect of the bronchial obstructing material is the increased work of breathing that results from the increased pulmonary tissue viscous and airway resistance as well as the diminished compliance. The latter is a result of many factors such as: Interstitial congestion, increased pulmonary vascular pressure, and increased pulmonary blood volume. The fact that dyspnea is not relieved when 100 per cent oxygen breathing results in normal or nearly normal oxygen saturation and that dyspnea is either corrected or greatly improved almost invariably upon administration of IPPB I with oxygen indicates that the dyspnea is not arising solely from the anoxia *per se* but largely from those factors that are responsible for increasing the work of breathing. Anoxia may well play a minor role in increasing respiratory drive. The increased work of breathing becomes part of a vicious cycle as illustrated in Figure 1 where resulting dyspnea increases metabolic demand and cardiac in-flow

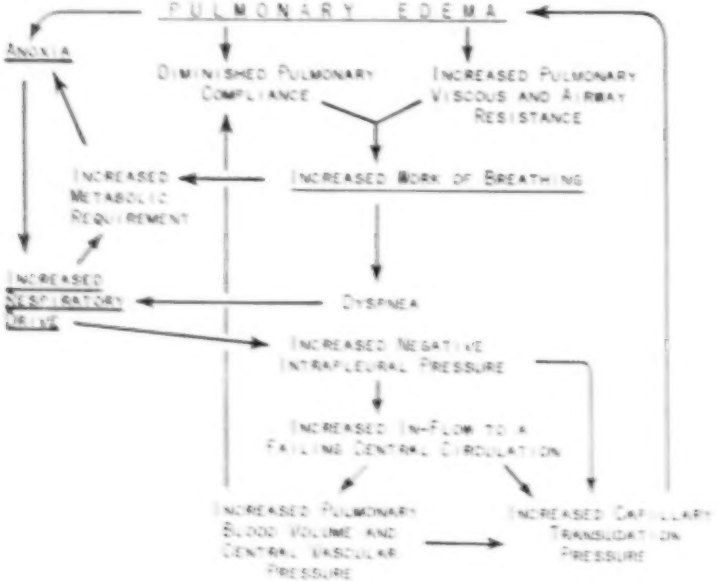

FIGURE 1

load. The latter increases central blood volume in a failing circulation and also increases capillary transudation pressure, both of which cause even further pulmonary change leading to a greater or continued increase in the work of breathing.

Thus, methods of treatment which attack this system are indicated for pulmonary edema. The role of oxygen is obvious under these circumstances. Morphine effectively decreases respiratory drive and this is doubtless its principal value regardless of whether this is effected by direct depression of the respiratory center or by diminishing psychic over-stimulation accompanying the fearful attacks. Anti-foaming agents effectively decrease the resistance to airflow by diminishing the obstructing effect of the bronchopulmonary fluid, and thus are clearly crucial in disrupting this cycle. Other therapeutic agents[15-17] often used may be indirectly effective in combating certain disturbances shown in Figure 1 but their importance is relatively less pertinent to this discussion.

On the other hand, oxygen and bronchodilator detergent aerosols administered by IPPB/I perhaps with the addition of anti-foaming agents by nebulized mist is the singularly most effective approach to the interruption of the self-perpetuating pathophysical disturbance since it provides a safe, immediate approach to both anoxia and the increased work of breathing. Figure 2 summarizes the effects of IPPB/I in patients with pulmonary edema.

The mechanisms of the development of hypotension or shock in pulmonary edema are not clearly elucidated. It is likely that eliminating anoxia was important in correcting hypotension in the cases presented. However, general improvement in the central circulation with increased cardiac output may be an even more important factor.

The role of improved lymphatic function, which is largely dependent on adequate ventilation and which has been emphasized by Drinker[5] and more

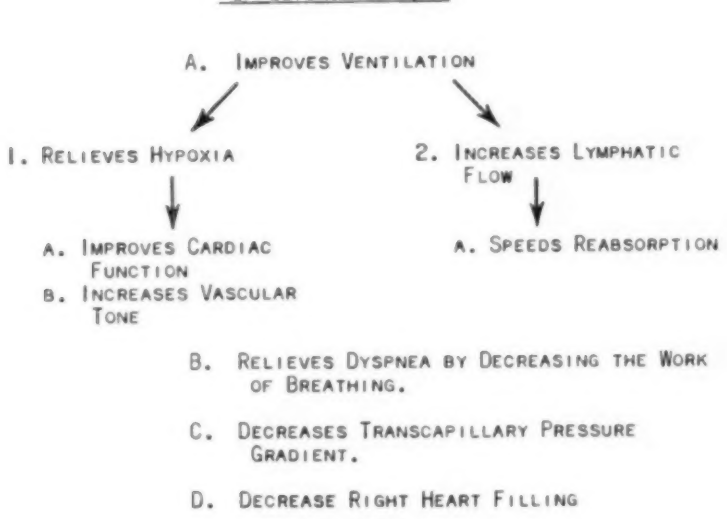
EFFECTS OF IPPB/I
A. IMPROVES VENTILATION
1. RELIEVES HYPOXIA
2. INCREASES LYMPHATIC FLOW
A. IMPROVES CARDIAC FUNCTION
B. INCREASES VASCULAR TONE
A. SPEEDS REABSORPTION
B. RELIEVES DYSPNEA BY DECREASING THE WORK OF BREATHING.
C. DECREASES TRANSCAPILLARY PRESSURE GRADIENT.
D. DECREASE RIGHT HEART FILLING

FIGURE 2

recently by Courtice,[18] deserves special mention since IPPB/I is not only capable of improving ventilation but at the same time decreases the transcapillary pressure gradient and cardiac filling that would otherwise rise with increased depth of respiration by voluntary effort.

SUMMARY

Pulmonary edema, regardless of etiology, is characterized by severe dyspnea owing to acute hypoxia and profound increase in the work of breathing with acute ventilatory insufficiency. Not infrequently, hypotension or shock are also present. Treatment preferably should be directed at the etiology, but the urgency of the situation often seems to contraindicate any delay for diagnostic procedures. Oxygen and bronchodilator detergent aerosol administered by positive pressure breathing, inspiratory (IPPB/I-O_2), with or without anti-foaming agents, have been demonstrated to be a safe, rapid method of correcting the physiological disturbances including shock, while more deliberate and precise diagnostic procedures are undertaken to elucidate the etiology of the attack.

RESUMEN

El edema pulmonar cualquiera que sea su etiología, se caracteriza por disnea severa debida a hipoxia aguda y aumento intenso del trabajo de la respiración con insuficiencia ventilatoria aguda.

El tratamiento debe dirigirse a la etiología pero la urgencia de la situación a menudo parece contraindicar cualquier retardo debido a los procedimientos de diagnóstico. Administración de oxígeno a presión positiva inspiratoria (IPPB/I-O_2) con o sin angentes antiespumantes es lo que ha demostrado ser un método seguro y rápido para corregir los trastornos fisiológicos que incluyen el shock mientras procedimientos más deliberados y precisos se ponen en práctica para aclarar la etiología del ataque.

RESUME

L'oedème pulmonaire, sans tenir compte de son étiologie, est caractérisée par une dyspnée sérieuse, due à un importante manque d'oxygène, et à l'augmentation marquée de l'activité respiratoire avec insuffisance aiguë de la ventilation. Il n'est pas exceptionnel de noter également de l'hypotension ou un état de shock. Le traitement devrait être de préférence étiologique, mais l'urgence de la situation contre-indique souvent l'attente qu'entraineraint des investigations diagnostiques. L'oxygène administrè sous pression positive inspiratoire, associé ou non à des produits "antibuées," s'est montré être un procédé rapide et sans danger pour corriger les perturbations physiologiques, y compris le shock. Pendant ce temps, on peut mettre en train les techniques plus perfectionnées et plus précises de diagnostic, qui permettront d'élucider la cause de l'attaque.

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A Study of Re-treatment Cases vs Original Treatment Cases of Pulmonary Tuberculosis*, **

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A primary problem in the current treatment of pulmonary tuberculosis is the ever-increasing number of patients who have had interrupted periods of antimicrobial therapy. The chemotherapeutic era in tuberculosis now extends well over 10 years. Re-exacerbations are occurring, particularly among the early, inadequately treated patients. Quite as importantly, case-finding efforts are spreading to include the elderly, homeless, indigent, alcoholic whose instability precludes long-term, continuous therapy.

To assess the impact of these changing conditions upon modern treatment, it was decided, therefore, to analyze the consecutive admissions over a two-year period in this large municipal sanatorium with particular attention to possible differences in the background of original and repeat admissions, their response to treatment and the time factor in such differences as were found to exist.

Material and Methods

During the two calendar years from January 1, 1955 to December 31, 1956, 1213 adult males were admitted to William H. Maybury Sanatorium: 712 as original, 501 as retreatment patients. Fifty of the total group were found to be non-tuberculous, 25 had extrapulmonary disease, leaving 1138 with pulmonary tuberculosis for analysis. Of these, 643 (56.5 per cent) were original treatment and 495 (43.5 per cent) were repeat treatment cases, hereinafter referred to as "originals" and "repeats," respectively.

Originals, by definition, were virgin treatment cases. Repeats included two types: 1) those who had received prior antituberculosis drug therapy with known interruption of more than 21 days, and 2) transfers to the sanatorium among whom continuity of therapy could not be established. Abscondees with less than three weeks' interruption of therapy were returned to classification with the originals.

The backgrounds of the two groups of patients were studied as regards age, color, vocation, marital status, alcoholism, complications, classification and duration of disease, cavitation, sputum status, and types and numbers of prior admissions. Response to treatment in the sanatorium was measured at six-month observation periods in terms of x-ray change, cavity closure, sputum conversion, and success or failure in reaching treatment objectives. Finally, comparison of the status of the two groups was made at the point of latest sanatorium observation, December 31, 1957 or before when discharge, transfer or death terminated the hospital stay.

All patients received the types of antimicrobial therapy commonly used in the sanatorium during 1955-56 (i.e., various combinations of isoniazid,

*Wm. H. Maybury Sanatorium.
**Presented at the 24th Annual Meeting, American College of Chest Physicians, San Francisco, June 18-22, 1958.

PAS, and streptomycin, with additional preparations in cases of poor response or in problems of research). No attempt is made in this presentation to evaluate differences in response to various chemotherapeutic regimens or to follow the fate of the patients in the post-sanatorium period. Attention was directed to differences between originals and repeats at various periods of in-sanatorium observation with particular attention to the timing and significance of such differences as were found to occur.

Background Data

Age: The average age of all adult admissions in 1955-6 was 50.13 years. The originals averaged 51.1 years, the repeats 48.9 years. There were slightly lower percentages of originals in age groups through 64 years but 8 per cent more in the bracket of 65 and over.

Color: Three-fourths of the entire group were white: 77 per cent of the originals and 73 per cent of the repeats. In general a higher proportion of the older men were white, of the younger men non-white.

Vocation: Four-fifths of the total group were unskilled laborers: 79 per cent of the originals and 83 per cent of the repeats.

Marital Status: There was striking difference in the marital status of the two groups. Thus 58 per cent of the originals were unmarried (single, separated, divorced, or widowers) while nearly three-fourths (73.5 per cent) of the repeats were unmarried. This significant difference illustrates the recognized stabilizing influence of the wife and home on the behavior of hospitalized patients. Conversely the relatively more unstable repeater had experienced little more success in maintaining his home and marriage than in dealing successfully with the problems surrounding his tuberculosis.

Alcoholism: Here again there was marked difference in the background of the two groups. Nearly half (49.9 per cent) of the repeats but only one-quarter (28 per cent) of the originals were alcoholics. Alcoholism is defined here as the repeated excessive use of alcohol before or during hospitalization. It was a severe disciplinary problem, a serious impediment to cooperation, and a major factor in the frequent breaks in continuity of treatment among the repeats.

Complications: The presence of associated extrapulmonary tuberculous disease was about 7 per cent in each group, but non-tuberculous complications (silicosis, diabetes, non-pulmonary malignancy, gastric resection and other) totalled 11.6 per cent among the originals, only 4.5 per cent in the repeats. Pulmonary emphysema was prevalent in both.

Classification of tuberculous disease: The classification of pulmonary disease revealed less group difference than had been anticipated. On admission 10 per cent of the originals had minimal, 41 per cent moderately advanced and 49 per cent far advanced disease; among the repeats there were 6 per cent with minimal disease, 39 per cent moderately advanced and 55 per cent far advanced. In general the repeats had somewhat more fibrotic disease than their original treatment cohorts.

Cavitation: The admission chest films of 65 per cent of the originals and 58 per cent of the repeats were read as showing cavitation, reflecting in the latter group the effect of prior treatment. Fewer cavities of both small and large size were recorded among the repeats. Thirty-seven per

TABLE I
PATIENTS UNDER SANATORIUM OBSERVATION IN EACH PERIOD

Months	Original	Repeat	Total
6	643	495	1138
12	424	283	707
18	262	184	446
24	111	96	207
30	44	61	105
30+	11	17	48

cent of the originals and 34 per cent of the repeats had cavities less than 4 cm. in total diameter. Cavities totalling 4 cm. or over were recorded in 27 per cent of the originals and 24 per cent of the repeats. Presence of cavitation and the size thereof are based on the reports of roentgenologist Carl C. Birkelo, M.D.

Sputum Status: Surprisingly, 71 per cent of the originals and only 48 per cent of the repeats were positive directly or by culture on admission studies. This is again a reflection of prior treatment, some of it recent, among the latter group.

Types of Prior Discharge: Of the repeats, 17 per cent had been discharged with approval from a tuberculosis sanatorium many months to several years previously. Sixteen per cent had been transferred from another institution but with interruption of treatment sometime previously; 67 per cent had absconded from the institution of prior treatment.

Number of Periods Prior Treatment: Thirty per cent of the repeats had had three or more periods of prior treatment and 5 per cent had had six or more hospitalizations; one patient had had 13 prior periods of therapy. The majority however (70 per cent), had had only one or two previous periods of treatment. As noted previously, periods of less than 21 days out of the hospital were not counted as interruptions of treatment.

Time Elapsed since First Treatment: The chronicity of disease among the repeat patients was outstanding. In half of this group (51 per cent) more than two years had elapsed since their disease had first been treated and one-fourth (24 per cent) had had their disease for more than five years. Eleven per cent had received collapse therapy, four per cent resectional surgery and three per cent thoracoplasty.

The typical repeat treatment patient, then, was a white man, 49 years of age, unskilled, unmarried, alcoholic, with positive sputum and far advanced fibro-cavitary disease of two years' duration, an abscondee with one or two periods of previous therapy. The original treatment patient on the other hand was slightly older, also unmarried, non-alcoholic, with slightly less extensive, more exudative disease.

Comparison of Results

Observations on roentgenologic and bacteriologic changes and the status of the patients were made at six-month intervals after the beginning of therapy on all patients remaining in the sanatorium. Table I lists the number of patients by group and in total, under sanatorium observation

TABLE II
DISCHARGED WITH APPROVAL
(Per cent of patients under observation)

Months	Original		Repeat		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
6	31	5	40	8	71	6
12	38	9	22	8	60	8
18	39	15	9	5	48	11
24	18	16	9	9	27	13
30	3	7	3	5	6	6
30+	0	0	1	6	1	2

during each period. The status of the patients' roentgenologic and other changes was further recorded at the date of last observation in the sanatorium, December 31, 1957 or before. Using these two methods of evaluation, marked differences as well as certain similarities in the results of treatment were observed in the original and repeat treatment patients.

Periodic Observations

In this section dealing with periodic observations, cumulative figures obviously are impossible due to the attrition in both groups from discharge, transfer, death, and absconding. In Tables I to III and Figures 1 through 4 the numbers listed at six-month intervals relate specifically to the numbers of patients under observation in each period. Attention is thus focused on the fate of remaining in-sanatorium patients.

Discharge and Surgical Transfer—Objective Reached

Interesting differences between the two groups are seen in the rates of discharge and surgical transfer, the two categories of "objective reached." Originals remaining in the sanatorium are discharged with medical approval at an increasing rate up to the 24th month (Table II). A sizeable number of repeats are discharged early, this group being made up largely of erroneously suspected relapses and abscondees who had been nearly ready for discharge before leaving the institution, but the rate drops off rapidly after the 12th month.

Early surgical transfers (Figure 1) among repeats consist largely of patients who accept surgery after readmission, having absconded previously to avoid it. After 18 months, however, surgical salvage among repeats is extremely low. In contrast, originals remaining in the sanatorium continue to be brought to surgery in high proportion even up to 30 months.

Absconded: The proportion of abscondees among the repeats was roughly twice that of the originals (Table III) reflecting a continuance upon readmission of previously demonstrated behavioral patterns and attitudes. Alcoholism, emotional instability and marital separation are

TABLE III
ABSCONDED
(Per Cent of Patients under Observation)

Months	Original		Repeat		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
6	70	11	130	26	200	18
12	56	13	66	23	122	17
18	33	13	39	21	72	16
24	12	11	13	14	25	12
30	3	7	14	23	17	16
30+	0	0	1	6	1	2

important factors in the difference in abscond rates. Ninety per cent of absconds in both groups leave within the first 18 months after admission; among repeats, about half the absconds are within the first six months.

Deaths: Marked differences between the two groups are apparent in an analysis of deaths. Eighty-six deaths from all causes occurred among the 1138 patients under observation, 56 (9 per cent) among the originals and 30 (or 6 per cent) among the repeats.

Non-tuberculous causes accounted for 33 (38.4 per cent) of the deaths, 23 of these deaths occurring among the originals and 10 among the repeats. In order of frequency, extrapulmonary carcinoma, renal disease, pneumonia, pulmonary embolism, cardiac disease, pulmonary carcinoma and cerebrovascular accidents were causes of non-tuberculous deaths.

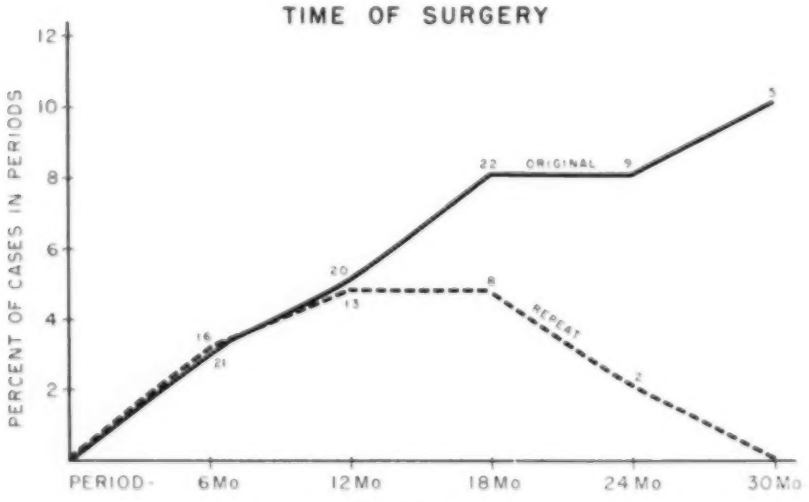

FIGURE 1

There were 53 deaths from pulmonary tuberculosis, 33 among the originals and 20 among the repeats.

The time factor in deaths is of interest. Of the 86 deaths from all causes in both groups, 48 (56 per cent) occurred within three months after admission, 59 (60 per cent) within six months and 76 (88 per cent) within the first 12 months after admission.

Twenty-six (76 per cent) of the 33 deaths from pulmonary tuberculosis among the originals occurred within the first three months following admission, which we interpret as being due to overwhelming disease on admission resulting in death of the patients before antimicrobial therapy could be effective. Only six (30 per cent) of the 20 tuberculous deaths among the repeats, however, occurred within the first three months. Significantly, during later months of hospitalization only seven deaths (24 per cent) occurred among originals and 14 (70 per cent) among the repeats. Thus, percentage-wise, deaths after three months of therapy occurred nearly three times as frequently among the repeats. The twin factors of bacillary resistance and ineffective chemotherapy in the repeats are important here.

Sixty per cent of all tuberculosis deaths in the series occurred in the first three months of hospitalization; 48 per cent of all non-tuberculosis deaths also occurred in this period.

X-ray Change: One of the most striking differences between the two groups lies in the degree and rate of x-ray change. As seen in Figure 2, at each time interval a far greater proportion of originals showed moderate or marked x-ray improvement. More repeats showed slight or no improvement. An alarmingly greater proportion of repeats showed x-ray worsening during the later observation periods. These differences relate directly to the more exudative nature of original treatment lesions and to breaks in continuity of therapy and excessive bacillary resistance in the repeat group.

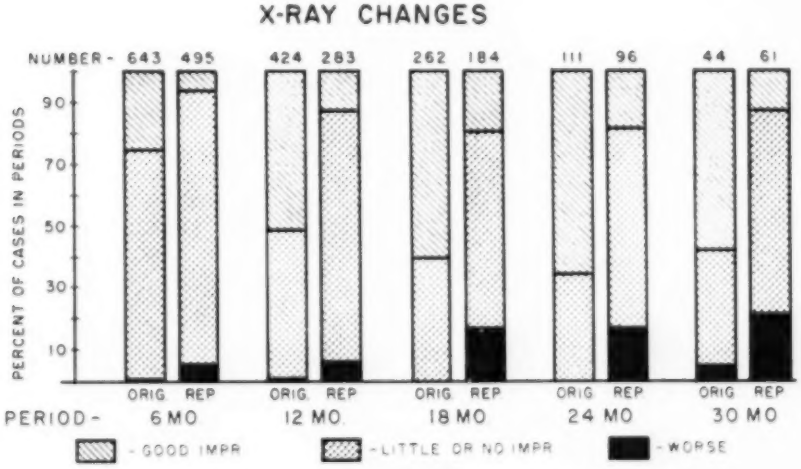
X-RAY CHANGES
NUMBER - 643 495 424 283 262 184 111 96 44 61
PERCENT OF CASES IN PERIODS
90
70
50
30
10
ORIG REP ORIG REP ORIG REP ORIG REP ORIG REP
PERIOD - 6 MO 12 MO 18 MO 24 MO 30 MO
- GOOD IMPR
- LITTLE OR NO IMPR
- WORSE

FIGURE 2

TABLE IV
CAVITY CLOSURE
(Per Cent of Admission Cavities)

	Original		Repeat		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
	All Sizes					
Closed in 12 months	155	37	70	24	225	32
Closed after 12 months	31	7	9	3	40	6
	Under 4 Cm.					
Closed in 12 months	115	50	58	35	173	44
Closed after 12 months	13	6	6	4	19	5
	Over 4 Cm.					
Closed in 12 months	40	21	12	9	52	16
Closed after 12 months	18	9	3	2	21	7

Cavity Closure: There is important difference, too, in the number of cavity closures. Period by period, a significantly higher proportion of the originals still under observation closed their cavities (Figure 3). Half of the number of cavities in both groups which eventually were to close had done so by the sixth month. The proportion of closed cavities at that time, however, was twice as high among the original treatment patients (23 versus 13 per cent).

Table IV lists data regarding cavity closure in the two groups in relation to time and cavity size.

The 12-month time interval was critical as regards cavity closure. Thirty-two per cent of all cavities in both groups had closed by the 12th month; only six per cent closed thereafter. This is an all-important factor to be considered in timing surgical intervention.

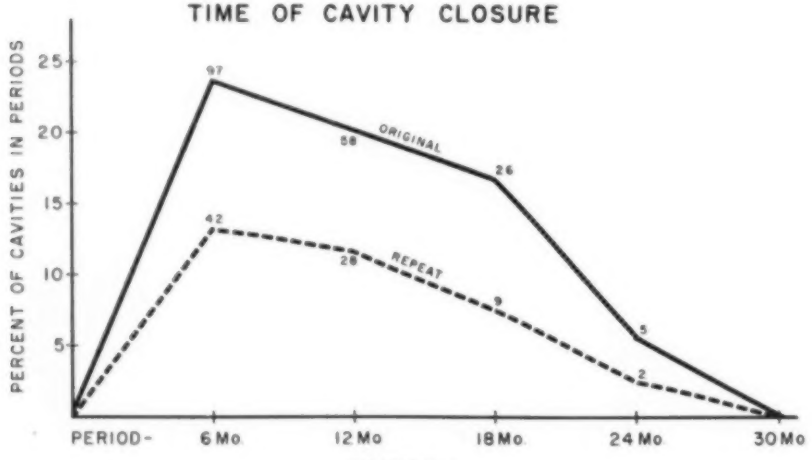

FIGURE 3

Total diameter of cavities on admission related inversely to eventual cavity closure. Thus, 49 per cent of all cavities in both groups under 4 cm. closed without surgery but only 23 per cent of those over that diameter. Regardless of cavity size, significantly less cavity closure occurred among the repeats (44 versus 27 per cent).

Sputum Conversion: Period by period, a considerably higher percentage of sputum conversions occurred among the originals still under observation (Figure 4). This difference was somewhat less marked, however, than were x-ray changes and cavity closure.

The bulk of sputum conversions had occurred by the sixth month; the 12-month period was critical in this regard. Sixty-eight per cent of all admission-positive patients converted their sputum by the 12th month, but only 5 per cent thereafter. This again is an important factor in timing surgical intervention.

Bacillary Resistance: At all periods of observation, a high percentage of positive-sputum repeat patients yielded tubercle bacilli resistant to one or more of the major antimicrobials (Table V). Moreover, the proportion of positive-sputum repeats with resistant bacilli was significantly higher at each time interval than was the case with the originals. This undoubtedly played an important role in the differential response to therapy. After 18 months, however, practically all positive patients in both groups were resistant to the major antimicrobials with which they had been treated.

Final Status

The preceding analysis has dealt with periodic observations on the two groups of patients at six-month intervals during their course of treatment. Even more informative in pointing up differences in response to therapy is the analysis of the status of the patients at the last point of observation in the sanatorium, December 31, 1957, or before.

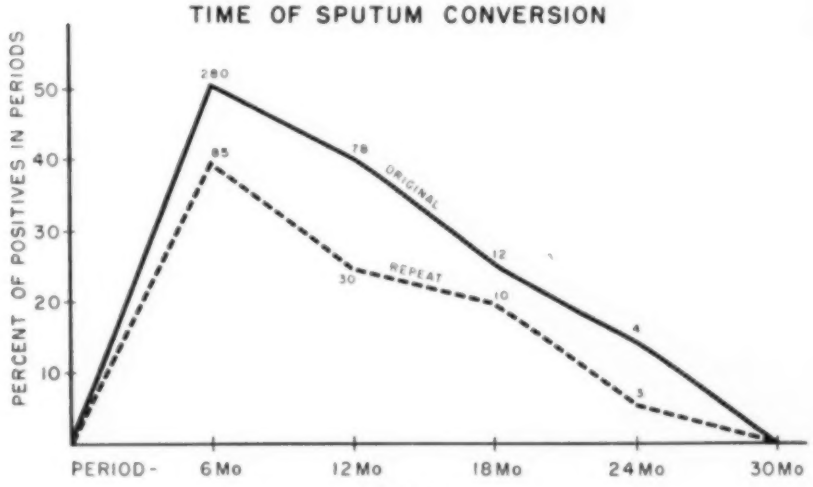

FIGURE 4

TABLE V
BACILLARY RESISTANCE
(Per Cent of Positive-Sputum Patients under Observation)

	Original		Repeat		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Adm.			70	14		
6 months	30	22	75	54	105	39
12 months	21	45	50	76	71	63
18 months	21	75	42	82	63	80
24 months	11	100	19	87	30	91
30 months	7	100	14	88	21	91
30 months plus	1	100	6	100	7	100

Final Status: Figure 5 shows the status at last observation of the 643 originals and 495 repeats. Twenty per cent of the former and 17 per cent of the latter had received their discharge. As noted before, a sizeable proportion of the repeat treatment group received early discharge because of failure to verify erroneously suspected re-exacerbation and because many had been nearly ready for discharge when they had previously absconded. Twelve per cent of original treatment patients were transferred for surgery, only 7 per cent of the repeats, a significant and important difference. Thus the twin objectives of discharge or surgical transfer were reached in one-third of the originals (32 per cent) and in only one-fourth (24 per cent) of the repeat group. Approximately equal proportions of each group (32 and 30 per cent respectively) were in the sanatorium or had been transferred for non-surgical reasons.

Death occurred in 9 per cent of the original treatment and 6 per cent of the repeat treatment patients. These figures relate directly to the

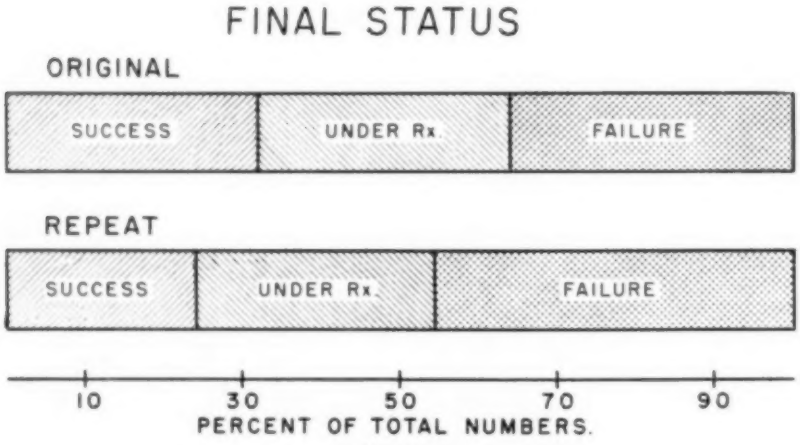

FIGURE 5

acute, pre-terminal condition of many first admissions and the more chronic disease of the average repeat admissions. Absconding was far more prevalent among those with previously interrupted therapy. Forty per cent of the repeat group absconded, frequently more than once, while only 27 per cent of the originals left against advice. Failure in therapy (death and absconding) thus occurred in 36 per cent of the originals and 46 per cent of the repeats.

X-ray Change, Final: One of the most pronounced differences in results of therapy is seen in the degree of x-ray change at last observation (Figure 6). Moderate to marked x-ray improvement occurred in 40 per cent of the originals but in only 11 per cent of the repeats; zero to slight improvement occurred in 59 per cent of originals, versus 83 per cent of repeats. X-ray worsening was observed in 6 per cent of repeats but in only 0.2 per cent of the originals. Again these figures relate to the more exudative nature of the disease, to better patient cooperation and to less frequent bacillary resistance in originally treated patients.

Cavity Status, Final: There were definite differences as regards cavity closure and diminution in cavity size (Figure 7). At the start of therapy 35 per cent of the original and 42 per cent of the repeat cases showed no cavitation; on final observation 66 per cent of the original and 60 per cent of the repeat patients had no cavities. At last observation a comparable percentage of patients in both groups had cavities under 4 cm. in total diameter. Among the originals, as a result of treatment, there was marked reduction in the number of patients with persistent cavitation greater than 4 cm.; this response was much less marked among the repeats.

Significantly, nearly half (44 per cent) of all original treatment cavities closed under medical therapy, only a quarter (27 per cent) of all retreatment cavities did so. Nearly three times as many large cavities (4 cm. or over) closed among original as among repeat cases. In both groups, however, no cavity larger than 7 cm. was observed to close nor did cavities close with total diameter greater than 7 cm.

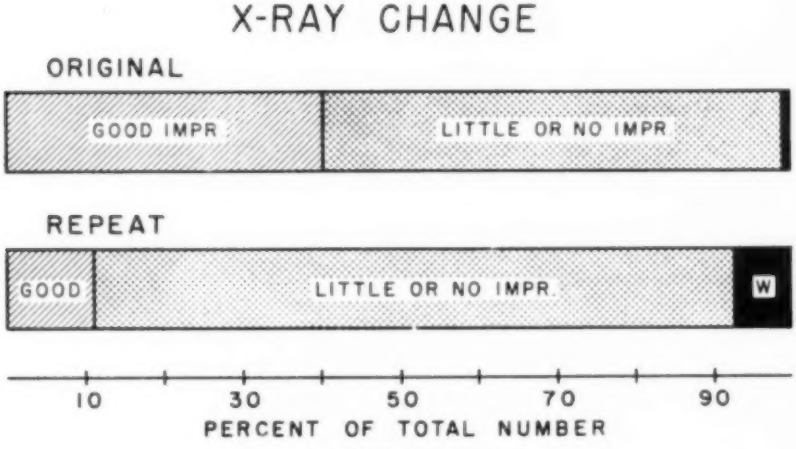

FIGURE 6

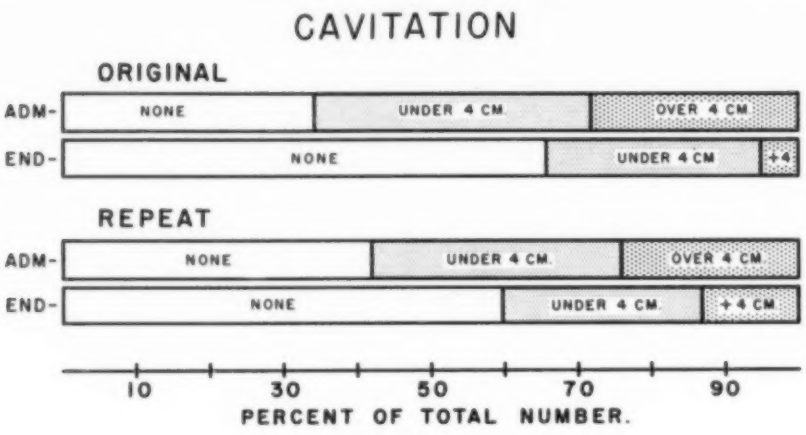

FIGURE 7

The fate of cavities which did not close is of interest. In original treatment cases only 3 per cent of cavities (all sizes) enlarged but in the repeats 9 per cent of small cavities (under 4 cm.) and 15 per cent of large cavities (4 cm. or over) became larger. Moreover, cavity enlargement among the originals was frequently associated with negative sputum and clearing of infiltrations—the result of excavation of caseous areas. In the repeat group, however, cavity enlargement was associated for the most part with x-ray worsening, positive sputum and bacillary resistance, constituting real progression of disease.

Sputum Status, Final Observation (Figure 8): At the beginning of therapy, 71 per cent of the original and 48 per cent of the repeat cases were positive on direct examination and/or culture. At last observation 13 per cent and 20 per cent, respectively, remained positive, a creditable response in both groups. Significantly, however, sputum conversion occurred in 81 per cent of the admission-positive originals and only 58 per cent of the admission-positive repeat cases.

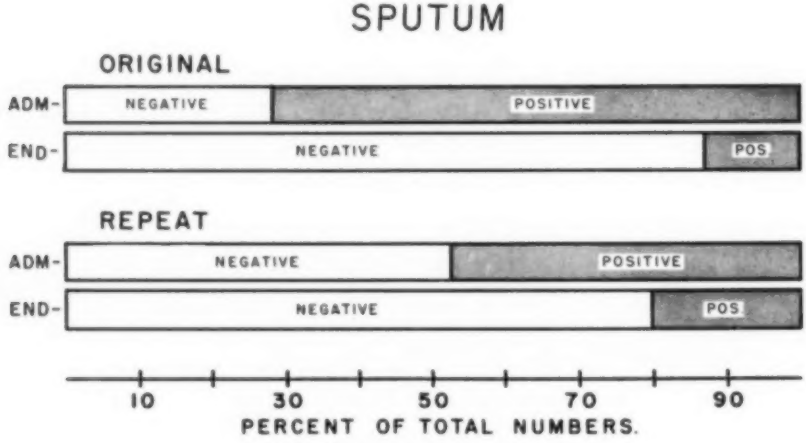

FIGURE 8

TABLE VI
BACILLARY RESISTANCE VERSUS CAVITATIONS

	Original		Repeat		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
No cavitation	3/218	1	2/196	1	5/ 414	1
Cav. orig. < 4 cm. remaining open	4/ 91	4	16/100	16	20/ 191	10
Cav. orig. > 4 cm. remaining open	17/109	16	46/102	45	63/ 211	30
Cav. orig. < 4 cm. closing	3/123	2	1/ 63	2	4/ 186	2
Cav. orig. > 4 cm. closing	0/ 56	0	0/ 15	0	0/ 71	0
TOTAL	27/597	4.4	65/476	13.7	92/1073	7.8

Of the 124 original treatment patients still in the sanatorium December 31, 1957 only six (4 per cent) were still positive. Of the 93 repeat patients who still remained, 24 (26 per cent) were still positive. All 30 of these patients were resistant to the major antimicrobials.

Bacillary Resistance: In both groups development of bacillary resistance was directly proportional to the size and persistence of admission cavities (Table VI). Resistance was negligible when cavities closed but mounted rapidly when cavities remained open, particularly those of large diameter. Moreover, resistance developed three to four times as frequently in the retreatment patients and militated against their clinical recovery.

DISCUSSION

With the advent of generally accepted regimens of antimicrobial therapy for original-treatment patients, the problem of the patients with prior periods of therapy assumes major medical importance.

Nor is this a static problem. Nearly half of the adult admissions to Maybury Sanatorium (and doubtless to other large metropolitan sanatoria) are prior-treatment patients, and the percentage increases year by year.

Several factors are responsible for this increase in repeat admissions. Case finding efforts now extend to the lower strata of society: to the indigent, homeless, unskilled, unmarried alcoholics whose experiences have left them restless, rebellious and mobile. Also contributory, though in minor proportion, are breakdowns among early inadequately-treated patients.

Paradoxically, antimicrobials contribute in themselves to the problem of retreatment. Chemotherapeutic agents are sufficiently effective to preserve and prolong life but are not sufficiently effective to prevent in all cases the later necessity for retreatment. Moreover, chemotherapy, particularly in its early days, has made difficult the attainment of mature surgical judgment.

From the standpoint of native host resistance, retreatment cases are a select group. Despite multiple breaks in therapy continuity, these individuals constitute a portion of the survivors from a somewhat larger group of initially treated patients, many of whom succumbed to their tuberculous disease. As shown in this study, the retreatment case is less positive, more resistant, less cavitary and more fibrotic and so less likely to respond to therapy. Important, too, are certain human traits presented by these retreatment patients which make them less cooperative and less conscientious in regard to treatment. Notwithstanding these facts the degree of success in treating these repeat cases is reasonably acceptable, due mainly to therapy regimen manipulation and to surgery. But failures are prominent and possibly contribute toward keeping the retreatment problem from becoming unduly excessive.

The value of judicious antimicrobial therapy is shown by the sputum conversion rate among the retreatment positives, but this is not paralleled by cavity closure or

x-ray resolution. Thus there is generated at the same time both the physician's reluctance toward discharge and the patient's sense of false security, leading eventually to discharge against advice. Eternal patient education thus becomes a necessity.

Bacillary resistance to antimicrobials is a much more serious factor in retreatment patients and contributes measurably to lack of improvement or worsening and to the higher death rate from tuberculosis in this group after three months. The relationship of bacillary resistance to unclosed cavities should be a warning to employ surgical measures at the earliest time indicated in persistent cavitary cases: before the 12th month if possible, after which few cavities in our series closed without surgery. This thought applies even more emphatically in cavities over 4 cm. in diameter.

As compared with the original treatment cases in this series, the retreatment patients showed: less x-ray resolution, cavity closure and sputum conversion; and more x-ray worsening, bacillary resistance and deaths after three months' treatment. It is obligatory, therefore, to:

a) Prevent original treatment patients from becoming retreatment patients. It is almost axiomatic that breaks in therapy continuity contribute measurably and primarily to failure in achieving treatment objectives.

b) Keep retreatment patients under therapy. Although palpably less than ideal, the results of therapy in retreatment patients are reasonably acceptable.

c) Use maximally effective initial chemotherapy to obtain early sputum conversion and avoid antimicrobial resistance.

d) Employ surgical measures early in the presence of persistant cavitation.

e) Give cardinal place to the various attentions needed to reduce the rate of absconding. Admittedly, with the recalcitrant fraction of our sanatorium populations increasing, enlistment of patient interest and cooperation is discouragingly difficult. Successful effort along these lines is mandatory, however. On the national level increasing attention is being given to the combined problem of tuberculosis and alcoholism. Prominent, too, are the increased efforts toward better measures of rehabilitation. Such advances, however, must find application at the individual level in an effort to capture the interest of the disinterested patient. Education, understanding, tolerance, firmness, all must play a part. Only to the extent that all patients are brought and kept under antimicrobial therapy for adequate periods can they be either cured or maintained in an acceptable degree of negativity.

SUMMARY

Significant differences in background and in treatment response were noted in 643 original and 495 retreatment patients admitted with pulmonary tuberculosis to Wm. H. Maybury Sanatorium during the calendar years 1955 and 1956. The typical retreatment patient was unskilled, alcoholic, with far-advanced fibrocavitary disease of two years' duration, an abscondee with one or two periods of previous therapy; his original treatment counterpart had slightly less extensive, more exudative disease and more stable personality traits. In roentgenologic clearing, cavity closure, sputum conversion and attainment of discharge or surgical transfer, the retreatment patient lagged far behind; he experienced more x-ray worsening, bacillary resistance and late death from tuberculosis. Notwithstanding, the degree of success in treating the repeat case is reasonably acceptable. To obtain maximal success, it is obligatory to use chemotherapy of highest initial impact, employ surgical measures early and give cardinal place to the various attentions needed to reduce the rate of absconding.

RESUMEN

Se encontraron diferencias significativas en los antecedentes y en los resultados del tratamiento en 643 enfermos originalmente atendidos y en 495 tratados por segunda vez, admitidos con tuberculosis pulmonar en el Sanatorio Maybury durante los años de 1955 y 1956.

El enfermo de readmisión era el tipo trabajador no especializado, alcohólico, con tuberculosis muy avanzada fibro-cavitaria de dos años de duración, de los que rheuían la continuación del tratamiento en dos o tres períodos anteriores; los otros, tratados por primera vez, con lesiones ligeramente menos extensas, con mayor factor exudativo, y más rasgos de personalidad estables. En lo que se refiere a limpieza radiológica, cierre de cavernas, conversión de esputos, y logro de alta o paso a cirugía, el enfermo de tratamiento renovado, se quedó mucho atrás del de tratamiento primitivo; se observó en él más frecuente empeoramiento radiológico, más resistencia bacilar, y muerte tardía por tuberculosis.

Sin embargo, el grado de éxito en el tratamiento del enfermo de repetición es aceptable razonablemente. Para obtener el máximo de resultados es obligatorio usar la quimioterapia de acción más intensa, emplear los procedimientos quirúrgicos pronto y dar importancia capital a los que sea necesario para evitar que se rehuya el tratamiento.

RESUME

Les auteurs notèrent des différences marquées aussi bien dans leur état que dans la réponse au traitement chez 643 malades traités pour la première fois et chez 495 autres traités de façon itérative, tous ayant été admis pour tuberculose pulmonaire au Sanatorium W. H. Maybury, pendant les années 1955 et 1956. Le type de malade traité pour la seconde fois était inadapté, alcoolique, atteint de tuberculose fibro-cavitaire très avancée, datant déjà de deux ans, et ayant interrompu une ou deux périodes de traitement antérieur le malade se présentant pour la première fois avait une affection légèrement moins extensive, plus exsudative, et une personnalité plus stable. Les résultats du malade qui avait rechuté étaient nettement moins bons au point de vue des progrès radiologiques, de la fermeture cavitaire, de la négativation de l'expectoration et du moment où l'on pouvait envisager la sortie de l'hôpital ou le transfert dans un centre chirurgical; on pouvait constater une aggravation radiologique plus fréquente, une résistance bacillaire et finalement la mort pour tuberculose. Néanmoins, la proportion de succès dans le traitement de ces cas à rechutes n'est pas trop mauvaise. Pour en obtenir le maximum, il est nécessaire d'utiliser la chimiothérapie à des concentrations plus élevées que lors des traitements précédents, d'avoir recours à des mesures chirurgicales précoces, et de donner une place capitale aux diverses surveillances nécessaires pour réduire le taux des abandons spontanés de la thérapeutique.

ZUSAMMENFASSUNG

Es wurden beträchtliche Differenzen im Charakter und in der Reaktion auf die Behandlung beobachtet bei 643 erstmals und 495 zu wiederholten Malen behandelnden Kranken, die während der Kalenderjahre 1955 und 1956 mit Lungentuberkulose in das Wm. H. Maybury-Sanatorium eingegiesen wurden. Der typisch rückfällige Patient war der ungelernte Arbeiter, mit Alkoholismus und weit fortgeschrittener fibrocavernöser Erkrankung von 2-jähriger Dauer, ein Drückeberger mit ein oder zwei vorausgegangenen Behandlungsmethoden; sein erstmals behandelter Gegenspieler hat einen um ein Geringes weniger ausgedehnten, aber dafür mehr exsudativen Befund und mehr ausgeglichene Charakterzüge in seiner Persönlichkeit. Hinsichtlich der röntgenologischen Rückbildung, Cavernenschrumpfung, Sputumkonversion und Erreichung von Entlassung oder Verlegung zur Operation blieb der rückfällige Patient beträchtlich zurück; bei ihm kam es häufiger zu röntgenologischen Verschlechterungen, Bazillenresistenz und späterem Tod an Tuberkulose. Nicht destoweniger ist das Ausmass des Erfolges bei der Behandlung von rückfälligen Kranken billigerweise als annehmbar zu bezeichnen. Um einen maximalen Erfolg zu erhalten, ist es obligatorisch. Chemotherapie von höchster initialer Schlagkraft einzusetzen, operative Massnahmen frühzeitig einzuleiten und den verschiedenen Gefälligkeiten einen kardinalen Platz einzuräumen, die erforderlich sind, um die Zahl der Kurabbrüche zu verringern.

Surgery of the Definable X-ray Lesion in Apparently Healthy Military Personnel

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In the military service periodic physical examinations given for a wide variety of purposes continue to disclose large numbers of totally asymptomatic pulmonary lesions. For the most part these lesions are seen in the younger age group for the simple reason that there are relatively few individuals on active duty beyond the age of 55. The necessarily crowded living conditions aboard naval vessels make it mandatory that all suspicious roentgenographic findings be subjected to the closest possible scrutiny as potential sources of tuberculosis infection, and the greater potential hazard of undiagnosed pulmonary lesions in the military establishment as compared to the civilian community can be readily appreciated. The purpose of this study is to present the authors' method of managing presumptively benign asymptomatic pulmonary lesions in military personnel.

The presence of an asymptomatic lesion in a routine roentgenogram of the chest may significantly affect military careers, for the United States Naval service where attrition rates for promotion are in the range of 25 per cent, the presence of an undiagnosed pulmonary abnormality may possibly reflect unfavorably on an officer's physical fitness for promotion. Again it may result in untimely admissions and readmissions to the sick list, thus interrupting career planning, often at crucial periods. Although promotion of naval personnel may not be effected during admissions to the sick list for observation or treatment, correction of the disability by surgical or other means reverses the presumption of unfitness.

At the time of separation from the service, an asymptomatic pulmonary lesion may be revealed which would ultimately become a liability in civilian life and surgical correction of this defect facilitates the transition. In the event correction of the defect is not feasible the individual must usually be retired for service-connected disability with retirement benefits.

Suspicious or abnormal chest x-ray film findings are usually considered to be disqualifying for enlistment, but unfortunately many recruits still are enlisted in rural stations where facilities for roentgenograms are unavailable. Under these circumstances enlistees are already well into recruit training with a federal expenditure of $2000.00 or more, before chest x-ray films are accomplished. Existing law allows immediate separation of these recruits without obligation to the Federal Government. Occasionally a minimal lesion is overlooked on initial examination and is discovered only after a prolonged interval, at which point the individual

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may have become a valuable specialist or perhaps even completed a professional course such as flight training, in which instance the investment in time and federal money is considerable. Even though review of prior films establishes that the lesion existed prior to entry, it becomes expedient to salvage as many of these cases as possible for continued active service.

Materials and Methods

Patients are channeled to the United States Naval Hospital, San Diego, from several sources: (1) The Naval and Marine Corps Recruit Training Centers, (2) outlying shore establishments of the Eleventh Naval District, (3) Army and Air Force installations as far east as New Mexico, (4) active units afloat representing perhaps 70 per cent of the Pacific Fleet, (5) The First Marine Division and Air Wing, and (6) The Third Marine Division in the Western Pacific. In all, this represents a clinical source of some hundreds of thousands of healthy young men, from which this series has largely been drawn. In addition to the foregoing active duty personnel, many members of the Fleet Naval Reserve, a group of men in their 40's who have served 20 years in active service and are retained at part pay until full retirement, reside in the San Diego area. Another substantial segment served by this hospital is made up of some 200,000 dependent wives and children, a few of whom are included. Finally, this Naval Hospital hospitalizes approximately 110 Veterans Administration patients, and a few cases from this group are included in this series.

In the period from January 1, 1955 to December 31, 1956 a total of 840 major thoracic surgical procedures, exclusive of cardiovascular surgery, were performed. Of these, 102 were for purely asymptomatic pulmonary lesions, all of which had been discovered at the time of periodic physical examination or in the course of hospitalization for unrelated illness. The isolated symptom of cough, elicited as part of the medical history but not volunteered as a specific complaint, was not considered to be disqualifying for this series, but asymptomatic cases of previously proved pulmonary disease and all pulmonary metastases of known neoplasms, even though

FIGURE 1

FIGURE 2

Figure 1: Coccidioidal cavity in right apex.—*Figure 2:* Congenital absence of right pulmonary artery.

primary and metastasis were both asymptomatic, were excluded. Chest pain, hemoptysis, weight loss, pleural effusion or the past history thereof, were disqualifying, as were all other local or constitutional symptoms or signs possibly relatable to the x-ray film lesion. No restriction was placed on the type of pulmonary pathology presented, so long as the patient appeared to be healthy and offered no complaint. In this respect the present study from many of the important recent contributions to the literature where attention has been directed primarily to a particular type of radiographic abnormality.

Most patients with asymptomatic undiagnosed chest lesions are admitted to a separate medical ward devoted to the preoperative study and late postoperative convalescence of such cases. Routine studies include cultures of sputum and gastric contents for acid-fast bacilli; tuberculin, coccidioidin and histoplasmin skin tests; posteroanterior, lordotic and lateral roentgenograms of the chest, bronchoscopy, blood count, erythrocyte sedimentation rate, and urinalysis, electrocardiogram, pulmonary function tests and serum electrolytes. At the time of bronchoscopy, additional cultures from bronchial washings are taken and, when indicated, cytological smears are made with pledgets of Gelfoam®. When appropriate, and this is true with nodules and parenchymal infiltrates, laminograms are made, which aid substantially in the identification of calcification in lesions that reveal no calcium content on conventional films. Unsuspected areas of cavitation may likewise be demonstrated by this technique. Supraclavicular fat pad biopsies are occasionally done but are not the rule in this series of asymptomatic patients. When the histoplasmin or coccidioidin skin test is strongly positive, appropriate serological studies are requested from the Fifth Army Medical Laboratory.

Excised tissue is submitted for routine gross and microscopic pathologic study. Sections of granulomatous lesions are stained by three methods: Hematoxylin and eosin, periodic acid-Schiff, and Ziehl-Nielson. Most, though not all, have been cultured for M. tuberculosis and smears made of caseous material for acid-fast bacilli. A relatively small number have been cultured for fungi.

Pathologic Diagnoses

Table IA shows the distribution of pathologic diagnoses returned on surgical specimens submitted for histologic study. The largest group, nonspecific granuloma, includes a number of related diagnoses, such as "caseous necrosis," "epithelioid granuloma" and "fibrocaseous granuloma," a descriptive term for a lesion which, after study reveals no etiologic agent. Tuberculous etiology was demonstrated by a combination of methods in more than a fourth of granulomatous lesions resected, 10 by culture and 13 by identification of acid-fast bacilli in tissue sections or on direct smears of caseous material. Coccidioides immitis was demonstrated in 16 per cent of the lesions, two of which were cavitary. Three explorations were carried out without evidence of gross pathology, a blind biopsy in one case being reported as "fibrous tissue with lymphatic hyperplasia." Combined bronchogenic carcinoma and tuberculosis was reported in one case, bronchiolar carcinoma in one case. Histoplasma capsulatum was identified twice. There was one case each of lipoid granuloma, bronchial adenoma, hamar-

toma, congenital absence of right pulmonary artery with hypoplasia of the lung, congenital cystic disease of the right upper lobe, sequestration of the left lower lobe, simple pericardial cyst, chronic empyema, and exostosis from a fractured rib.

When calcified nodules were grouped separately, the search for an etiologic diagnosis yielded considerably fewer positive findings. In a group of 39 lesions, 27 (70 per cent) were nonspecific granuloma, 9 (22.5 per cent) were coccidioides immitis, there was one (2.5 per cent) each of H. capsulatum and tuberculosis, and in one case (2.5 per cent) exploration revealed no gross abnormality.

Age

The ages ranged from 12 to 65 years; the youngest was the daughter of a naval officer and the oldest, who was a veteran patient, had a pericardial cyst. The distribution reflects fairly accurately the age of military service, most of the patients being in the third decade, with an arithmetical average of 32.2 years. Positive diagnoses were distributed uniformly through the several age groups. In 64 cases in which previous x-ray films were available for study, the known duration of lesions ranged from three months to 23 years, with an average of 2.8 years.

TABLE IA
PATHOLOGIC DIAGNOSES RETURNED ON 99 RESECTED SPECIMENS

Diagnosis		No.	Per Cent
Granuloma		89	90
Nonspecific	48		
Tuberculosis	23		
Coccidioides	15		
Histoplasma	2		
Lipoid granuloma	1		
Hamartoma		1	1
Bronchial Adenoma, carcinoid type		1	1
Chronic Empyema		1	1
Bronchogenic Carcinoma		1	1
Alveolar Cell Carcinoma		1	1
Sequestration LLL		1	1
Congenital Cystic Disease RUL		1	1
Pericardial Cyst		1	1
Exostosis from Fractured Rib		1	1
Fibrous Tissue		1	1
Total		99*	100

*Three cases explored without submission of a surgical specimen.

TABLE IB
RESULTS OF PATHOLOGIC STUDY OF 39 CALCIFIED NODULES

Nonspecific Caseous Granuloma	27
Histoplasma	1
Coccidioides	9
Tuberculosis	1
No Gross Lesion on Exploration	1
Total	39

Surgical Procedures

In this group of 102 patients, 105 procedures were performed by 15 different members of the resident and regular surgical staff. Because of the localization of most of the nodular lesions, the most frequent procedure was subsegmental reaction, either simple enucleation, in which the lesion is dissected out of the lung and the vascular and bronchial structures leading into it are ligated and divided as they are encountered, or wedge resection over forceps with closure of the lung proximally prior to excision. According to the preference of the individual operator, the defect left by enucleation may be obliterated and the pleura closed, or it may be left entirely open. Objections have been raised to closure of such a defect because of the possibility of subpleural emphysema or of fibrosis of the hematoma that forms within it. Neither of these complications has been observed in this series. It has been noted, however, that residual roentgenographic abnormality may persist at the site of closure for weeks or months as the locally encapsulated operative reaction is absorbed. When the site is left open the immediate roentgenographic result is more pleasing. Wedge resection of small subpleural lesions was performed 13 times. Most of these were done early in the course of the study, and enucleation is presently preferred. There were 27 segmental resections and 10 lobectomies, the majority for lesions described radiographically as infiltrates and cavities, but occasionally what was considered to be a small nodule was found on exploration to be an infiltrative process, involving much more of the lung than was suspected. Under the heading of multiple resections are four cases in which segmental resection and subsegmental resection were performed at the same time. One of these and one other required re-exploration for the control of postoperative hemorrhage. Three patients were subjected to exploration only, two of them having no demonstrable gross pathology at the time of surgery, and one presenting congenital absence of the right pulmonary artery which was unsuspected prior to operation. One patient had a 5 cm. inward-projecting exostosis at the

TABLE II
SURGICAL PROCEDURES PERFORMED ON 102 PATIENTS

Subsegmental Resection	53
Segmental Resection	27
Lobectomy	10
Exporatory Thoracotomy with Drainage of Hemothorax	2
Combined Resections*	4
Radical Pneumonectomy	1
Lung Biopsy	1
Mediastinal Node Biopsy	1
Excision of Exostosis	1
Excision of Pericardial Cyst	1
Decortication	1
Exploration only†	3
	105

*Segmental and Subsegmental Resection.
†One case of congenital absence of pulmonary artery. Two cases with no grossly demonstrable disease.

site of an old rib fracture at the costochondral junction, which was excised. In one case a simple cyst of the pericardium extending into the right lower lung field was excised. One decortication of an ancient empyema was performed. One patient was subjected to radical pneumonectomy for carcinoma and another was explored and determined to be unresectable by reason of invasion of the ribs and brachial plexus, the diagnosis of bronchogenic carcinoma being established by biopsy of an enlarged mediastinal node.

Postoperative Care

Postoperative management has been standardized to a high degree to facilitate nursing care, much of which is administered by highly competent and well motivated Hospital Corps personnel. Blood loss is measured at surgery and replacement is given in excess of the measured loss.[9] A specimen of blood is drawn on the ward for a hemoglobin determination immediately after the patient returns from surgery and is repeated daily until after thoracotomy tubes are removed. An immediate portable chest x-ray film is made and repeated daily until the tubes are out, usually on the fourth postoperative day, at which time the patient is taken to the x-ray department where technically more perfect posteroanterior and lateral views are made. These are repeated at increasing intervals thereafter. All cases are drained by No. 24 or No. 26 F rubber intercostal tubes, one for the subsegmentals and two or three for the more extensive procedures. One or two are placed in the seventh intercostal space at the midaxillary line and a third one, if employed, is placed in the second interspace at the midclavicular line. These are connected to underwater suction drainage with a Chaffin-Pratt pump. Penicillin and streptomycin are administered routinely, and oral antituberculotic drugs when indicated are commenced on the first postoperative day. About the eighth postoperative day most patients are returned to the medical service to complete their convalescence. This arrangement has proved to be most satisfactory, for it serves to maintain a small ward census on the surgical service and allows the maximum of nursing attention to be directed to the management of small numbers of acute problems.

For patients in whom the diagnosis of tuberculosis is established or presumed, which includes most of the non-specific granulomas, INH 300 mg. and PAS 12 Gm. daily are continued for a period of 18 months after surgery. Patients return to duty after five or six months total hospitalization and continue medication in a duty status.

Radiographic Interpretation

For purposes of this study the radiographic appearance of most of the parenchymal abnormalities has been grouped under three general headings: nodule, infiltrate and cavity. A few others are described more in detail as they presented themselves. A nodule here, as in other series, is a sharply circumscribed, more or less rounded radiodensity, surrounded by normal lung. It has been necessary to establish a maximum size in this category because no nodule exceeded 3.5 cm. in size on x-ray film. Infiltrate refers to a parenchymal radiodensity generally irregular in outline and without clearly defined borders. The most commonly encountered lesion was the

nodule, of which there was a total of 57, 39 of these showing some degree of calcification on plain films or laminogram. There were 33 infiltrates which varied in size from 0.5 cm. to 7 or 8 cm. in diameter. In six cases a single cavity was described, and in one there were multiple minute cavities identifiable on tomogram. One case of combined bronchogenic carcinoma and tuberculosis had a medially placed cavity and a soft apical nodule. Pleural thickening was reported in one case of an old empyema. A pericardial cyst presented a smooth, rounded radiodensity in the right cardiophrenic angle extending into the lung. Decreased bronchovascular markings in the left base on plain x-ray film and absence of alveolar filling on bronchogram were reported in a case of sequestration of the left lower lobe. Multiple bullae in the right upper lobe were described in a patient with congenital cystic disease. The case of absence of the right pulmonary artery showed atelectasis of the right upper lobe and stenosis of the lobar bronchus.

Disposition

Follow-up on patients returned to duty has been adequate for the brief interval since treatment was completed; however, a number of retired personnel or personnel released from active service have been lost. To this time, of those returned to duty there has been no known late complication of surgery, except for one who complained of post-thoracotomy pain. There have been no known instances of reactivation or recurrency of tuberculosis. Recently it has become Navy policy to retain all surgically treated cases of proved pulmonary tuberculosis, who are not retired, in an administrative limited duty status for a period of three years, although persons with residual lesions not subjected to resection are separated medically. Limited duty amounts to the performance of all the duties of the member's rank, except that he is ordered to duty ashore at an activity near the Naval Hospital, night watches are curtailed and regular chest x-ray films and hospital visits are scheduled. Thus the patient's services

TABLE III

DISPOSITION OF 102 PATIENTS AFTER DIAGNOSTIC THORACOTOMY

ACTIVE DUTY MILITARY PERSONNEL (85)

	No.	Per Cent
Returned to duty	61	78.8
Disposition pending, return probable	6	
Retired	15	20.0
Disposition pending, retirement probable	2	
Died	1	1.2
	85	100.

INACTIVE AND SUPERNUMERARY PATIENTS (17)

	No.	Per Cent
Returned to Usual Work	12	7
Required Further Care at Home	5	29
	17	100

are fully utilized and he is at the same time maintained under satisfactory medical surveillance. Of considerable military significance has been the number of patients rehabilitated for continued active service by this program of resecting asymptomatic pulmonary lesions; furthermore it has increased the number of personnel leaving the service physically fit to obtain work in civilian life. Of a total of 85 active duty patients, 67 (78.8 per cent) were returned to duty, 17 were retired, 16 of them for pulmonary tuberculosis, but most of these retirements were effected prior to the implementation of the newer policy, and it is considered likely that they would now be returned to duty. One was separated for reason of complications directly attributable to the surgery. There was one postoperative death, the direct cause of which was not clearly defined at autopsy, in a case of congenital hypoplasia of the lung and absence of the pulmonary artery, explored for asymptomatic carcinoma. In the supernumerary group, numbering 17 in all, 12 returned to their usual work and five required additional restriction of activity and further treatment at home. Two of these were patients with carcinoma of the lung, one of whom was explored and found unresectable but is still living 16 months after surgery. This gives a surgical mortality of 1 per cent and a late mortality of zero per cent. In the total series 78 per cent returned to full usual work or may reasonably be expected to and 22 per cent required further treatment or died.

In Table IV are listed all major and minor surgical complications in the entire group of 102 patients. One single patient suffered multiple complications, namely postoperative hemorrhage, empyema, wound infection and bronchopleural fistula. Six of the seven cases who had a persistent air leak after pulmonary resection sealed spontaneously a few days later than usual. The only undesirable feature in all but one of these was the necessity of maintaining intercostal suction for the additional period. One required tracheotomy for control of respiratory distress incident to mediastinal and

TABLE IV
SURGICAL COMPLICATIONS IN 19 PATIENTS

Major Complications	5* Patients
Hemorrhage	2
Bronchopleural Fistula	1
Empyema	1
Wound Infection	2
Mediastinal Emphysema	1
Atelectasis	1
	8

*One patient developed wound infection, hemorrhage, bronchopleural fistula and empyema.

Minor Complications	14 Patients
Minimal Peripheral Air Leak	5
Pleural Effusion	4
Bronchospasm	1
Penicillin Reaction	2
Acute Gastric Dilatation	1
Wound Separation	1
	14

subcutaneous emphysema. One developed an air leak after leaving the hospital and was admitted a month later with pneumothorax and partial atelectasis on the operative side. This was managed by needle aspiration but an additional period of hospitalization was required. This patient, a 27 year old dependent wife, is well and strong at the present time. One of the cases of postoperative hemorrhage has been mentioned above; this complication, which required emergency thoracotomy the night of initial surgery, set off a train of difficulties which terminated only after the resulting empyema had been drained and lobectomy performed for bronchopleural fistula. The patient ended up with markedly diminished pulmonary function and was eventually retired from the Navy for this reason. Another postoperative hemothorax was opened the night of surgery and drained but this patient recovered without further incident. The source of bleeding was not definitely identified in either case but was believed to have occurred at the site pleural adhesions were dissected from the chest wall. Both wound infections were caused by a highly virulent M. aureus, requiring wide drainage and a long convalescence. The same organism, which was resistant to all antibiotics then in routine use, had previously been identified in a large number of breast abscesses and surgical wound infections, of which there had been an epidemic in other parts of the hospital at that time.

An alarming instance of status asthmaticus occurred during surgery in a young officer who was undergoing nodulectomy. The right upper lobe was collapsed at the time of onset of bronchospasm, and an hour or more elapsed before any expansion could be obtained after release of bronchospasm was effected by changing the anesthetic agent from nitrous oxide to ether. Immediately after surgery the lobe appeared on x-ray film to be consolidated, but this finding cleared progressively and at the end of three weeks there was no discernible abnormality beyond the usual amount of postoperative reaction. Two severe penicillin reactions required steroid therapy. One case of acute gastric dilatation was recognized early and responded promptly to treatment. In one instance, on removal of sutures on the seventh postoperative day, there was dehiscence of the skin throughout the entire length of a thoracotomy incision, but healing was prompt and secure after secondary closure. Four cases developed a degree of pleural effusion after discontinuance of intercostal drainage, requiring needle aspiration one to three times. These were all of minor consequence and did not materially affect the course of convales-

TABLE V
RESULTS OF SKIN TESTS

Tuberculin (PPD 1 or 2) only	34
Tuberculin and coccidioidin	5
Tuberculin and histoplasmin	18
Coccidioidin only	6
Histoplasmin only	7
Coccidioidin and histoplasmin	4
PPD, histoplasmin and coccidioidin	8
Negative	5
TOTAL	87
Not tested or results not available	15

cence. There was no instance of progression, activation, or spread of tuberculosis after pulmonary resection; the single case of empyema was of a pyogenic variety, caused by the same organism responsible for the wound infections. Only five of the 19 patients whose postoperative course was complicated were considered to have incurred major problems which impeded convalescence. One was permanently disabled by a series of complications.

Skin Tests

Although the results of only 87 patients' skin tests are available for tabulation, it is known that nearly all of the 102 patients were tested. As mentioned earlier, the routine preoperative examination includes tuberculin (PPD intracutaneous), coccidioidin and histoplasmin skin tests, the results of which appear in Table V. In the military age group, more information may presumably be adduced from positive reactions than is otherwise possible, and several known conversions have been observed. One young patient was known to have converted in all three skin tests over a two year period, but his lesion was reported to be a nonspecific granuloma. In every case but one the pathological diagnosis of granuloma was accompanied by at least positive skin test. As in other similar studies, however, the five negatives were more significant than the 82 positives. Of these five, pulmonary sequestration was found in one, carcinoid adenoma was found in one, two were grossly negative on exploration and no specimen was submitted, and one was reported to be a nonspecific granuloma. Because of strongly positive coccidioidin reaction, serologic studies were requested in several cases and were reported to be positive in titers of 1:16 or greater in three instances. In only one of these was the organism demonstrable in the surgical specimen. There was one positive serologic test for histoplasmosis, but the organism was not found in the lesion resected in that case.

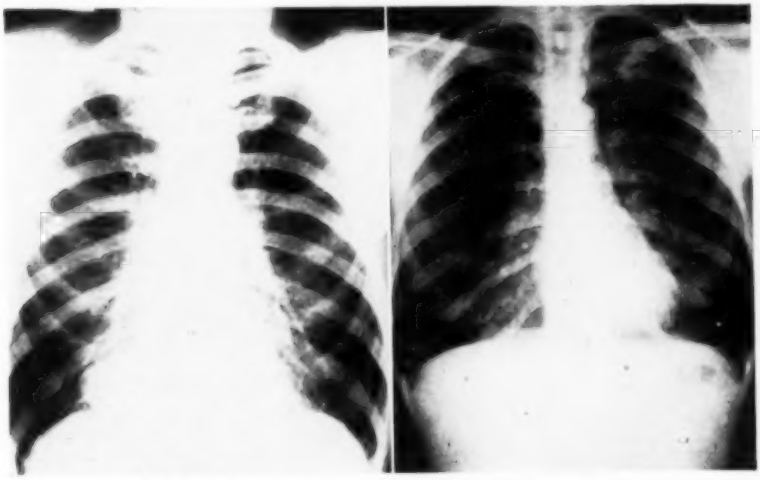

FIGURE 3 FIGURE 4

Figure 3: A pericardial cyst.—*Figure 4:* Alveolar cell ca left upper lobe.

Inspection of the pathological data shows immediately the great significance that age grouping plays in the distribution of diagnoses obtained in a series of pulmonary lesions subjected to resection.

Discussion

The inclusion of such a wide variety of radiographic entities and the selection of cases purely on the basis of absence of symptomatology makes this series less than exactly comparable to the studies of others[1-7] in which the independent variable has been a specific roentgenographic finding, usually the so-called coin lesion or the solitary pulmonary nodule. In an analysis of reported series totaling 1203 cases collected from the literature to which they added 215 of their own, Davis, Peabody and Katz[1] found an overall incidence of primary malignancy in solitary rounded lesions of the lung of 29.7 per cent. Considering the age group involved, in our study, and the requirement that symptoms be absent, the low incidence of carcinoma is not surprising. Jones and Cleve estimated, from a review of 369 cases in the literature, to which they added 14 of their own, that the incidence of carcinoma in solitary round pulmonary lesions in patients under 35 was 0.27 per cent.

Taking into consideration the group of 89 lesions collected under the general heading of granuloma, it is noted that 54 per cent were found to be of a nonspecific type, 26 were demonstrably tuberculous, 19 per cent were mycotic, and one was a lipoid granuloma. The bacteriology of resected lesions known to be tuberculous beforehand and treated medically for long periods preoperatively is presently the subject of much discussion and intensive study, and the present paper can offer nothing to further this important work. It is assumed, however, that a substantial percentage of the nonspecific granulomas were tuberculomas and it is considered appropriate to review briefly some of the current concepts of pathology and bacteriology of morphologically similar lesions known to be tuberculous. Most of the solid granulomas of unknown etiology resected in this study are considered to represent necrotic foci, either solid primarily or the end result of closure or inspissation of cavities. As such they might be considered "target point" lesions which have arrived at their present status without therapy, but as has been pointed out there has been little demonstrable difference in the bacteriology of these foci with antituberculotic agents or without.[11] The stage of healing appears to be the determining factor in the matter of the presence or absence of tubercle bacilli; uniformly caseous specimens contain the most culturable organisms, those with cholesterol crystals having fewer, and those which are laminated and contain large amounts of calcium salts being sterile in most instances. Attempts to grow acid-fast organisms from resected necrotic foci have been notably unrewarding, as have similar attempts to infect guinea pigs with digested and undigested, saline suspended, Tween-80-suspended and albumin-emulsified aliquots of caseous material. Disparity exists between the numbers of bacilli found on smear and the apparent infectivity of the specimen; lesions containing many acid-fast bacilli may be negative on culture and inoculation, while others in which morphological identification cannot be made will cause accelerated disease in guinea pigs and early, rapid growth on culture. In other instances only an indolent infection will appear in the animals, or some will be positive while others do not even show tuberculin conversion.[11, 12] From observations of the apparent sensitizing effect of finely particulate silicon on tuberculosis, silicon granulomas have been produced in animals and suspensions from surgical specimens injected therein, all without increasing the yield of positive growth. General experience at present indicates that approximately 5 per cent of necrotic tuberculous foci will contain culturable organisms.[14] By the use of a special culture medium containing bovine albumen, Hobby, Auerbach and associates were able to achieve a much higher percentage of positive cultures—21 out of 31—from closed necrotic foci, when the period of incubation was prolonged up to 284 days.[15] Some specimens were initially negative to animal inoculation but the material from the final positive cultures was uniformly pathogenic. In necrotic lesions the variability of distribution of organisms in different portions of the same lesion has been noted,[11] as have differences in growth characteristics and antibiotic sensitivity. A condition of dormancy or attenuation or subtotal death has been postulated, and this apparently occurs in the absence of antibiotics, being brought about presumably by tuberculostatic or tuberculocidal elements derived from tissue necrosis.[16] According to Medlar,[14] however, if the products of necrosis do not bring about lysis or destruction of the bacilli they may, for a time, multiply within necrotic foci, and he further suggests that the finding of large numbers of organisms within these foci indicates the source of relapse sometimes seen in patients arrested for years. Medlar is of the opinion that it is possibly incorrect to assume that because some bacilli are capable of growing on artificial media, all viable organisms should be able to do the same. An occasional patient whose resected lesion is determined to harbor avirulent or nonculturable organisms may, nevertheless, have subsequent progressive disease.[11] When several nodules are resected, some will prove to have viable bacilli while others will not; in cases where two or more lesions are

removed, the rate of positive cultures and inoculations is considerably higher than in the patient presenting a single focus. Altogether there is a general lack of solid agreement on the present fate of the tubercle bacillus in target-point lesions. Surely antimicrobial agents carry tuberculosis up to this point more rapidly than was previously possible, and many patients' lesions reach this stage of healing that might otherwise have remained in an open progressive state. After the focus encapsulates, however, it appears to be a function of natural endogenous forces to complete the destruction of the offending organism, a process which must occur in the majority of cases as will be inferred below. As stated by Dubos,[17] however, "No technique is yet available to bring about with certainty a complete eradication of the bacilli from infected tissue. Only the resistance of the host stands between reactivation and inactivity of disease caused by bacilli surviving here or there, detectable or not by classical methods of pathology and bacteriology."

The clinical behavior of tuberculomas, on the other hand, is a more palpable matter, and it is of practical importance to assess the potentialities of the necrotic tuberculous focus in the age group under consideration. Grenville-Mathers[18] observed 18 patients with 23 tuberculomas from five to 148 months, during which time four calcified, seven remained unchanged, five enlarged, four showed cavitation, and three cavitated with bronchogenic spread. Reviewing the experience of the Trudeau Sanitorium, Mitchell[19] calculated a relapse rate of 26.1 per cent in 40 patients followed from 4 to 22 years. It was stressed that serious or fatal relapses were rare. In a series of 7,105 mental patients with roentgenographic evidence of inactive tuberculosis at the time of admission to the hospital, Katz, Kunofsky and Locke[20] reported a general incidence of reactivation of 1.5 per cent per year over a 12 year period with a somewhat higher incidence under age 45. In a carefully controlled study conducted in the Army Medical Service by Waring and Roper,[21] 967 young army personnel (average age 28 years) with roentgenographic evidence of minimal tuberculosis were followed 100 per cent for an average of more than four years. Because the selection of cases commenced in 1944, the importance of mycotic infections in the production of chest x-ray abnormalities was less well appreciated than it is now, and the consequent lack of selection from this standpoint makes the series very comparable to our own. Of the original 967 patients 342 were, after appropriate study, determined to be asymptomatic and inactive at initial examination. A history of known active tuberculosis was elicited in 30 patients, but the remaining 312 may reasonably be compared with the 89 military patients presently under discussion. Periodic follow-up examinations were conducted over the years from January, 1944 to September, 1949. As this program was prolonged, more and more of the asymptomatic inactive cases broke down, and at the completion of the study a total of 75 relapses had occurred. Twenty-four per cent of 312 young men in military service who had asymptomatic minimal lesions on routine chest x-ray film later developed clinically active pulmonary or extrapulmonary tuberculosis.

In view of the foregoing, it is considered that the potentially dangerous nature of pulmonary granulomas must be presumed,[22-24] and the management of such lesions, therefore, becomes a matter of considerable importance in military service if the predictable relapse rate is to be prevented. Certain patients should probably be selected out, namely those presenting nodules which are significantly calcified. All evidence, bacteriologic, pathologic and clinical, points to the fact that these are essentially innocuous.[1] As pointed out, lamination and calcification are presumptive or sterility with respect to tuberculosis, and solid calcified coccidiomas and histoplasmomas are probably harmless. Hamartoma which is not uncommonly calcified, may when not the mechanical cause of symptoms, be left alone with impunity. Significant calcification in bronchogenic carcinoma is an extreme rarity and other malignant lesions which may be calcified, such as osteogenic sarcoma and chondrosarcoma are likewise quite uncommon. Fibro-calcific irregular infiltrates are likely to be less innocuous, and the other soft nodules and infiltrates should, in our opinion, be considered for resection in the young age group. There is no disagreement in this country regarding indications for diagnostic thoracotomy for pulmonary nodules in the age group beyond 35. Cavitary lesions, whatever the etiology, however stable, have shown a uniformly more serious rate of activity and bronchogenic reactivation and most will agree that they should be resected.

In most series a few useless operations will find their way into the figures. Limited to asymptomatic, undiagnosed roentgenographic findings, this study produced its fair share of phantoms in the form of three completely negative explorations and one exostosis projecting inward from the site of an old rib fracture. The uselessness of the last was debatable but the lack of symptoms made the indication at best doubtful.

In the military population, which moves so frequently, the chances of contracting one of the two common mycotic infections is great, as pointed out by Forsee and Perkins.[25] Six of our cases were non-calcified and, therefore, would merit resection for the usual reasons; of these, two were cavitary. Although the above authors report only 67 per cent positive coccidioidin skin tests in a series of 50 patients who underwent resection for coccidioidomycosis, all the cases in our series had a positive skin test. It is stated that less than 2 per cent of patients who contract the disease will develop caseous or cavitary lesions, and the frequency of unsuspected cavitation within ap-

parently solid necrotic coccidioidal foci is stressed. In the absence of any known satisfactory medical means of controlling spread of either coccidioidomycosis or histoplasmosis, resection of all non-calcified lesions is considered to be the treatment of choice.

SUMMARY

During the two year period from January 1955 through December 1956, 102 healthy asymptomatic patients with abnormal chest x-ray findings were subjected to exploratory diagnostic thoracotomy at the United States Naval Hospital, San Diego, California. In 89, instances a granuloma was found and excised; of these, 48 were nonspecific, 23 were tuberculosis, 15 were coccidioides, two were histoplasmosis and one was lipoid granuloma. Only two cases of carcinoma were encountered in the study, and it was presumed that the lower average age of 32 years accounted for the disparity between our experience in this regard and the reported experience of others. The remainder of the diagnoses included congenital absence of the pulmonary artery, bronchopulmonary sequestration, congenital cystic disease, hamartoma, adenoma, pericardial cyst, exostosis, and no disease. Whereas other studies yielding a high incidence of malignant neoplasms have stressed the importance of silent pulmonary nodules for the purpose of obtaining early diagnosis and significantly higher cure rates for carcinoma of the lung, the military population, being rather younger, appears not to harbor the large numbers of occult malignancies found elsewhere. In this younger segment, the potentially dangerous nature of the granuloma partially takes the place occupied by carcinoma at a later age, for although the 25 per cent reactivation predicted for such lesions rarely has a fatal or even serious outcome, the loss from active service of these individuals through disability retirement or prolonged hospitalization can be prevented by excision of the lesions at an early, asymptomatic, inactive time with minimal morbidity and mortality. Significant complications occurred in five cases, only one of which resulted in failure to return to full active service. There was one death due to postoperative shock of undetermined cause. Seventy-nine per cent returned to full service and as recent changes in Medical Department policy are implemented to take into account the favorable long-term results of combined medical and surgical management of pulmonary tuberculosis, it is believed that more than 90 per cent will be rehabilitated for continued active Naval service.

RESUMEN

Durante el período de Enero de 1955 a Diciembre de 1956, se sujetaron a toracotomía diagnóstica 102 individuos saludables y asintomáticos pero con hallazgos anormales a radiología torácica, lo que se llevó a cabo en el Hospital Naval de los Estados Unidos en San Diego, California. En 89 casos se encontró un granuloma que se extirpó; de éstos, 48 fueron no específicos, 23 tuberculosos, 15 de coccidioides, das de histoplasmosis, y uno era un granuloma lipóidico.

Solamente se encontraron dos casos de carcinoma en este estudio y se cree que la disparidad entre nuestra experiencia y la de otros, se debe a la edad baja media en el grupo que era de 32 años.

El resto de los diagnósticos fué de casos como ausencia congénita de arteria pulmonar, secuestración broncopulmonar, enfermedad quística congénita, hamartoma, adenoma, quiste pericárdico, exostosis y ausencia de enfermedad. En tanto que otros estudios que rinden un número importante de neoplasias malignas, han hecho resaltar la importancia de los nódulos silenciosos en el pulmón que deben investigarse para mejorar el diagnóstico temprano del carcinoma pulmonar, entre la población militar, que es relativamente más joven, parece que no hay una elevada frecuencia de enfermedades malignas neoplásicas que se ven en otros grupos. En este grupo más joven, la naturaleza potencialmente peligrosa del granuloma, ocupa el lugar que corresponde al carcinoma en otras edades porque, aunque el 25 por ciento de reactivación esperada para tales lesiones rara vez tiene un resultado fatal o aún severo, la pérdida de estos individuos como elementos activos del servicio por retiro debido a incapacidad o la hospitalización prolongada pueden ser evitadas por la excisión cuando son asintomáticas, inactivas y esa excisión da una morbilidad y mortalidad mínimas.

Hubo complicaciones de importancia en 5 casos, pero sólo uno trajo como consecuencia el dejar de volver al servicio activo.

Hubo una muerte debida a shock postoperatorio de causa indeterminada. Setenta y nueve por ciento regresaron a servicio activo y como los cambios de actitud recientes consideran la necesidad de tratamiento de largo plazo de la tuberculosis se cree que más del 90 por ciento se rehabilitarán para continuar el servicio naval activo.

RESUME

Pendant une période de deux ans allant de janvier 1955 à décembre 1956, 102 malades sans symptômes et bien portants, mais présentant des anomalies pulmonaires radiologiques furent soumis à une thoracotomie exploratrice dans un but diagnostique, à l'hôpital Naval des Etats-Unis de San Diego, Californie. Dans 89 cas, on trouva un granulome et on l'enleva; parmi ceux-ci, 48 étaient non spécifiques, 23 étaient tuber-

culeux, 15 étaient des coccidioidies, deux étaient une histoplasmose et un un granulome lipide. On ne trouva que deux cas de carcinome dans cette étude, et on présume que la moyenne d'âge assez basse de 32 ans entra en ligne de compte dans la disparité qui existe entre l'expérience des auteurs à ce sujet et les études rapportées par d'autres. Pour ces autres cas, le diagnostic fut celui d'absence congénitale d'artère pulmonaire, de séquestration bronchopulmonaire, de maladie kystique congénitale, d'hamartome, d'adénome, de kyste péricardique, d'exostose et enfin dans certains cas on ne trouva aucune affection. Tandis que d'autres études donnant un taux élevé de néoplasies malignes ont permis d'insister sur l'importance des nodules pulmonaires silencieux, pour le diagnostic précoce et l'élévation du taux des guérisons dans le cancer du poumon, la population militaire, étant plutôt plus jeune, semble ne pas comporter le grand nombre d'affections malignes occultes que l'on trouve ailleurs.

Dans cette série plus jeune, le granulome, affection dangereuse en puissance, prend partiellement la place occupée par le cancer à un âge plus avancé. En effet, bien que les 25% de rechutes prévues pour de telles lésions aient rarement une issue fatale ou même sérieuse, la perte de service actif qui, pour ces individus, résulte de leur arrêt pour infirmité ou de leur hospitalisation prolongée peut être évitée par l'exérèse des lésions alors qu'elles sont encore au stade précoce, asymptomatique et inactif: la morbidité et la mortalité sont alors minimes. Des complications graves survinrent dans cinq cas, l'un d'eux seulement évolua de façon telle qu'il fut impossible de reprendre un service actif. Il y eut une mort due à un choc post-opératoire de cause indéterminée. 79% reprirent un service normal. Comme des changements récents sont intervenus dans la ligne de conduite du Département Médical pour faire entrer en ligne de compte les résultats favorables éloignés du traitement médical et chirurgical associés de la tuberculose pulmonaire, on pense que plus de 90% des cas seront habilités à poursuivre leur service actif dans la Marine.

ZUSAMMENFASSUNG

Während des 2-jährigen Zeitabschnittes von January 1955 bis Dezember 1956 wurden 102 gesunde, erscheinungsfreie Kranke mit krankhaften Thorax-Röntgenbefunden einer diagnostischen explorativen Thoracotomie unterzogen im Staatlichen Marienekrankenhaus von St. Diego, Californien. In 89 Fällen fand sich ein Granulom, das entfernt wurde; von diesen waren 48 unspezifisch, 23 tuberkulös, 15-mal handelte es sich um Coccidioides, 2-mal um Histoplasmose und einmal um ein Lipoid-Granulom. Nur 2 Fälle von Carzinom wurden in der Untersuchungsreihe angetroffen, und es wurde angenommen, dass das niedrige Durchschnittsalter von 32 Jahren verantwortlich war für die Verschiedenheit unserer diesbezüglichen Erfahrungen und den von anderer Seite mitgeteilten Ergebnissen. Die restlichen Diagnosen umfassten angeborenes Fehlen der Pulmonal-Arterie broncho-pulmonale Sequesterbildung, angeborene Cystenkrankheit, Hamartom, Adenom, Pericard-Cyste, Exostose und kein krankhafter Befund. Während andere Untersuchungen, die ein häufiges Vorkommen bösartiger Neubildungen ergaben, die Bedeutung von stummen, pulmonalen Knoten hinsichtlich der Stellung einer frühen Diagnose und beträchtlich höheren Heilungsziffern für das Lungencarzinom betonten, scheint sich unter den Wehrmachtsangehörigen, die beträchtlich jünger sind, nicht die grosse Zahl von erworbenen bösartigen Veränderungen zu finden, die von anderer Seite gefunden wurden. Bei dieser jüngeren Bevölkerungsgruppe nimmt die potentiell gefährliche Natur des Granuloms teilweise den Platz ein, der in einem späteren Alter vom Carzinom besetzt wird, denn obwohl die für solche Herde vorausgesagten 25% Reaktivierungen selten einen letalen oder selbst schwerwiegenden Verlauf nehmen, kann das Ausscheiden dieser Leute aus dem aktiven Dienst infolge Pensionierung wegen Dienstbeschädigung oder überlanger Krankenhausbehandlung vermieden werden durch Excission der Veränderungen während eines frühen, erscheinungsfreien, inaktiven Zeitpunktes mit minimaler Morbidität und Mortalität. Beträchtliche Komplikationen ereigneten sich in 5 Fällen, von denen nur einer mit dem Unvermögen der Wiederaufnahme des vollen aktiven Dienstes endete. Es trat ein Todesfall ein durch postoperativen Schock aus ungeklärter Ursache. 79% nahmen ihren vollen Dienst wieder auf und nach den kürzlich erfolgten Änderungen in der Beurteilungsmethode der Sanitätsabteilung bei dem günstigen Spätergebnissen der kombinierten konservativen und chirurgischen Behandlung der Lungentuberkulose in Rechnung zu stellen sind, wird angenommen, dass mehr als 90% wieder instand gesezt werden, ihren aktiven Marinedienst fortzusetzen.

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Meticorten as Adjuvant Therapy in Chronic Pulmonary Tuberculosis with Emphysema

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Introduction

The action of prednisone on a group of active pulmonary tuberculosis patients was studied. Some unexpected effects were noted with Prednisone used as an adjuvant drug in the chemotherapy of chronic, pulmonary Tuberculosis. The effect of steroids in tuberculosis has been subjected to a great deal of experimentation and clinical study for the past several years. Controversy still rages as to its actual therapeutic value. The wide disagreement among qualified clinical workers is not surprising, when one considers the effect of steroids on host parasite relationships, the hormonal balance of the organisms, and more specifically, the action on connective tissue itself. Numerous previous studies have been primarily related to the effect of steroids on other forms of tuberculosis; meningeal and miliary tuberculosis and effusions.

This study was initiated to determine the therapeutic value of prednisone with anti-microbial drugs on patients with chronic active, pulmonary tuberculosis with emphysema.

Materials—Methods

Forty-four patients with chronic pulmonary tuberculosis were selected from the wards of Metropolitan Hospital. All had received at least two years of chemotherapy with no clinical or x-ray improvement. These were so-called "good chronics" and not terminal, as has been described in previous literature on this subject. Bacillary susceptibility was pre-determined in all cases. They were then equally divided into prednisone and control groups.

*Background Factors**

The age of the patients varied from 24 to 76 years with an average of 50. Forty-two patients were men and two were women. Race distribution presented 19 Whites, seventeen Negroes, seven Puerto Ricans, and one Chinese.

Thirty-four had far advanced pulmonary tuberculosis and 10 presented moderately advanced disease. Tubercle bacilli were present in all but three. All patients had clinical evidence of pulmonary emphysema.

Regimen

(1) Each patient was placed on a group of anti-tuberculosis drugs as determined by sensitivity studies. Drugs used were streptomycin, INH, aminosalicylic acid, cycloserine and viomycin. Twenty-two received, in addition, 20 milligrams of prednisone daily, in four divided doses.

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*See Table I.

TABLE I—BACKGROUND DATA

	Cases	Age		Sex		Race		Stage of Disease	
		Range	Mean	Men	Women	White	Other	Far Advanced	Moderately Advanced
Prednisone	22	29-76	54	21	1	9	13	15	7
Control	22	24-74	47	21	1	10	12	19	3

(2) X-Ray films done prior to therapy, then bi-weekly for two months, and monthly thereafter. Tomograms were done as indicated.

(3) Complete hematological, urine and liver function tests were performed bi-weekly. Similarly, blood sugar, urea nitrogen, serum potassium, sodium and chlorides were determined.

(4) Ventilatory function studies, including maximum breathing capacity and timed vital capacity were done monthly.

(5) Serial electrocardiograms and weekly body weight and blood pressure were recorded.

Therapeutic Results

The primary phase of this study was to determine whether prednisone produced any extension of the disease in these patients and to weigh these results against the hazards of induced hypercorticism.

(a) *Clinical*

Improvement was noted soon after starting therapy by eight patients. Ten remained unchanged. Four became worse, demonstrating increasing dyspnea, and/or early congestive failure. At the end of therapy, an average increase of 10 pounds in body weight was noted in 13 patients.

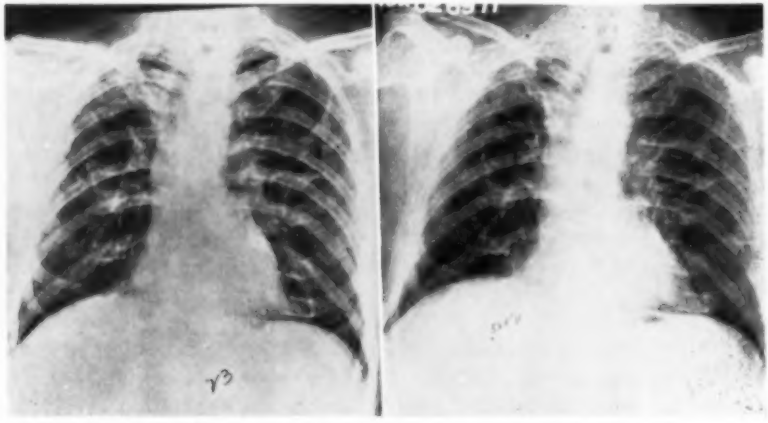

FIGURE 1 FIGURE 2

Figure 1: R. M. Roentgenogram of the chest taken just before prednisone therapy was begun, showing a fibro-caseous lesion of the right upper lobe with bi-lateral diffuse infiltrations.—*Figure 2:* Roentgenogram of the chest obtained after seven months of prednisone therapy shows minimal clearing of the pathology on both sides.

TABLE II—BACKGROUND DATA

	Cases	Duration of Treatment		Bacteriology		X-Ray Appearance	Emphysema	
		Range (Months)	Mean (Months)	Positive	Negative	Fibro-Caseous	Yes	No
Prednisone	22	2-10	5.5	20	2	22	22	0
Control	22	5-10	6	21	1	22	22	0

Nine lost an average of six pounds during the same period. Sixteen of the 20 controls showed no improvement or were worse. Four presented clinical improvement. Ten lost an average of eight pounds, while the other 10 gained an average of two pounds in this same period.

(b) *Bacteriology*

Twenty prednisone treated patients had tubercle bacilli in their sputa and two were bacilli free. After 24 weeks, 11 patients had bacilli in their sputa. Four did not complete the six month survey. Five had no tubercle bacilli in sputa on direct microscopy. Cultural methods did not reveal tubercle bacilli in two of these patients. Of the controls, at the end of 24 weeks, only two were bacilli free; the remainder were unchanged.

(c) *X-Ray Changes*

Fourteen patients showed no change roentgenographically in six months. Five improved. Of the remaining three, two demonstrated fresh exudative lesions. In one, steroid therapy was discontinued for disciplinary reasons, (unco-operativeness). The x-ray film lesions cleared within four weeks in both patients. Steroid therapy was maintained throughout this phase. The third prednisone treated patient demonstrated a progressively enlarging cavity, which to date, has persisted. There was no case of improve-

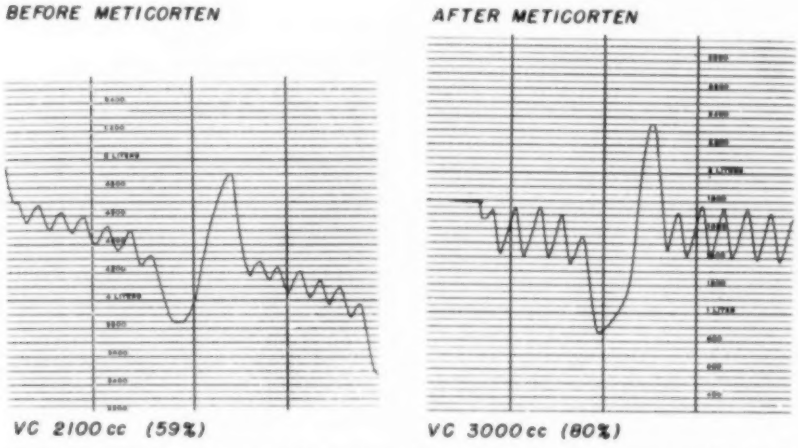

FIGURE 3: R. M. Spirographic tracing of vital capacity of the same patient before and after prednisone therapy. After 24 weeks of treatment, a 43 per cent increase in the vital capacity was observed.

TABLE III—RESULTS

		Clinical Improvement			Weight		Bacteriology		X-Ray Change		
	Cases	Improvement	No Improvement	Worse	Gain	Loss	Positive	Negative	Improvement	No Change	Worse
Prednisone	18	7	8	3	11	7	13	5	5	10	3
Control	20	4	11	5	10	10	18	2	0	19	1

ment noted roentgenographically in the controls, although 19 of 20 cases presented a fairly static x-ray film. There was one patient who developed an extension of disease during this control period.

(d) *Ventilatory Function*

Ventilatory function studies were done regularly on 15 patients for 24 weeks. Eight of these had an average increase of 25 per cent in vital capacity. Four presented no change as compared to pre-treatment values, while the remaining three showed a slight decrease.

Thirteen of the same 15 patients showed a substantial increase in their maximal breathing capacity. The average improvement observed was 41 per cent. The remaining two showed no change.

Ventilatory function studies done on the control patients presented no change in the vital capacity in 10 patients. Five showed an average increase of 10 per cent in their vital capacity and of these, only three showed a definite increase in their maximal breathing capacity. This average improvement was about 15 per cent.

(e) *Hemoptysis*

One unexpected and intriguing finding was the complete absence of hemoptysis in the prednisone patients. Ten of them had had a previous

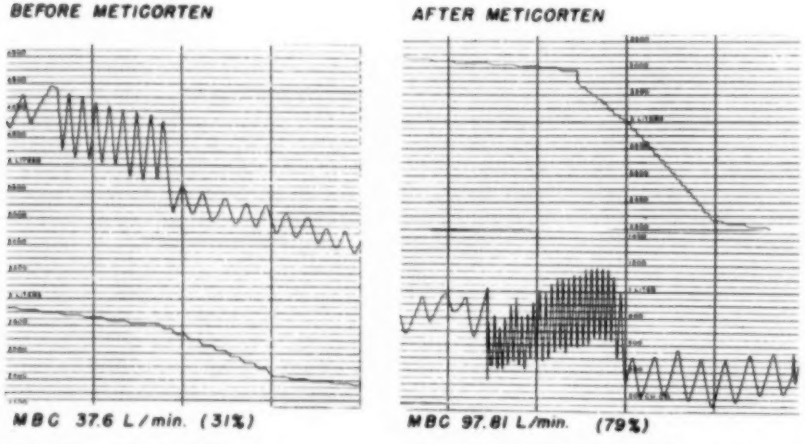

FIGURE 4: R. M. Spirographic tracing of maximal breathing capacity of the same patient. An increase of 163 per cent was observed in this patient after the 24 weeks of prednisone therapy.

history of repeated hemoptysis. None bled throughout therapy. One, who discontinued prednisone after 10 weeks, developed hemoptysis one month later. Nine of the 22 controls had varying bouts of hemoptysis. Two of these attacks were severe and exsanguinating, requiring blood replacement.

Toxic Reactions

1. *Carbohydrate Metabolism*

Two known diabetics of the prednisone group presented much more lability after steroids. One patient manifested persistent hyperglycemia and glycosuria, and in spite of doubling his insulin, prednisone had to be discontinued after two weeks of therapy.

Three other prednisone treated patients had a relative hyperglycemia, which was not treated and only one of these presented glycosuria which was transient.

2. *Electrolyte Metabolism*

Sodium and potassium levels remained unchanged. Serum chlorides were elevated in four patients. Urea nitrogen was elevated in two and serum calcium in one.

3. *Liver Function Tests*

Many of these patients had abnormal studies prior to institution of prednisone. (Many of our patients are chronic alcoholics.) No variation in cephalin flocculation, serum proteins or serum albumin was noted. Five developed progressive rise in serum globulin fraction.

4. *Cardiovascular System*

Serial electrocardiograms showed no changes as compared with pre-prednisone tracings.

FIGURE 5

FIGURE 6

Figure 5: H. W. Chest roentgenogram taken at the onset of prednisone therapy showing extensive tuberculous involvement of the upper two thirds of the left lung and infiltration of the right base. An old thoracoplasty can be seen on the right side.—*Figure 6:* H. W. Chest roentgenogram taken nine months after the start of prednisone therapy showed clearing of most of the pathology leaving a cystic area at the left upper lobe.

However, four developed cardiac decompensation, which responded to the usual regimen. No electrolyte changes were observed in these four patients.

5. *Formed Elements of Blood*

Marked leukocytosis was seen in 18 of the 22 patients. This developed within one week after prednisone therapy and has persisted to date.

Three showed a reduction in lymphocytes. Eighteen of the 22 had eosinophils prior to prednisone. After 24 weeks, only two of these showed the presence of eosinophils.

6. *Fat Metabolism*

Abnormal deposition of fat in the body characterized by "moon face" and/or "buffalo hump" were noted in two patients.

7. *Central Nervous System*

No euphoria was noted. Three patients complained of insomnia. This was controlled by giving the last dose of prednisone at 4:00 p.m instead of bedtime. Weakness of the lower extremities was noted by three patients.

Confusion and early schizoid reactions were observed in three. Concurrently, all three were receiving cycloserine and/or INH, either of which may produce similar symptoms.

Discussion of Steroid Therapy in Tuberculosis from the Point of View of Pathologic Physiology

Chemotherapy in recent years, has revolutionized the treatment of tuberculosis, but in the light of present knowledge and experience, chemotherapy certainly is not the answer for the eradication of the disease. Many factors are against it. The most important of them being the foci of caseous necrosis which alter the morphology of the bacilli and the fact that resting forms of bacilli escape the action of all antibiotics in use today. Clinical detection of the disease and its treatment thereof, before caseating occurs, is an unattainable ideal.

Thus, attacking this problem from a different point of view, seems meaningful. The anatomical and structural changes that can be produced by steroid therapy can so alter the conditions of bacterial nutrition and respiration as to stimulate the metabolic activity of the resting forms. This enhancement of the metabolic activity might stimulate these resting forms to multiply; thus making them amenable to antibiotics. A reduction in the number of resting forms in caseous lesions will in its turn, reduce the number of relapses.

Silver impregnation methods have demonstrated the presence of a fine network of reticulin fibers within all caseous lesions.[10] These probably are the precursors of collagen fibers and aid in fibroblastic proliferation. The action of cortico-steroids on connective tissue is well known.[8] It can be summarized as expressed by Albright in 1942, seven years before Hench and Kendall introduced the drug to clinical medicine; that its action is anti-anabolic, rather than catabolic. There is an increase in the urinary excretion of hydroxyproline, a failure of fibroblastic proliferation. But, where fibroblasts are already present, collagen and ground substances are normally laid down and immature connective tissue becomes mature.

The administration of prednisone might be expected to reduce fibroblastic activity in a growing lesion; thus reducing the extent of fibrosis with emphysema, a crippling complication. In a chronic lesion, a metabolic instability of the matrix with a consequent depolymerization might exert an action not unlike that of hyaluronidase. The loosening of the matrix as a result of depolymerization might enhance the diffusability of antibiotics as well as that of immune bodies to where the bacilli are enmeshed within the fibrous walls. In addition, sufficient nutriment and oxygen may reach the site at the same time, thus stimulating the multiplication of the resting bacilli. If one bears this in mind, it is not difficult to conceive why, in the absence of effective antibiotics to act at this stage of bacillary proliferation, steroid therapy can be potentially dangerous.

In a chronic disease such as tuberculosis, the part played by antigen antibody reaction cannot be underestimated.[10] Tuberculin allergy plays a decisive role in the evolution of the tubercle. The ability of the steroids to counteract all types of allergic manifestations at the cellular level is well known.[4, 6, 7] It has been definitely proven in animals that administration of steroids results in a considerable reduction of tuberculin sensitivity.[7] This probably occurs in man also, especially when one considers the action of steroids on lymphocytes and mast cells. Degeneration of lymphoid follicles and actual lysis of lymphocytes occur under steroid therapy.[9] This might partially account for the rise in serum protein,[2, 3] especially the globulin fraction. The theory that lysis of lymphocytes releases a flood of antibodies that are contained in them, has been discounted,[2, 3] but a certain rise in the titre of circulating antibodies does take place as evidenced by the fact that serial per-cutaneous tests with PPD have shown a decreasing amount of reaction.[1]

The presence of lymphocytes in great abundance at the site of chronic inflammation has given rise to a great deal of speculation.[10, 12] Their appearance at the same time as the development of hypersensitivity cannot be discounted as mere coincidence. Their exact function is still unknown but many workers have claimed that they are capable of transforming themselves into fibroblasts.[10, 12] If that is so, the advantage of reducing the number of lymphocytes becomes apparent at once. Mast cells contain a large proportion of pre-formed histamine and heparin and these cells, under steroid therapy, appear to lose their granules and degenerate. This decrease in heparin level in the circulating blood may be reason for the lowering of the coagulation time. This may explain the absence of hemoptysis in our group of patients.

Recently Handley[13] report similar findings in a small series noting the absence of hemoptysis in prednisone treated tuberculous patients.

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SUMMARY

A group of 22 patients with chronic, active, pulmonary tuberculosis with emphysema was treated with anti-tuberculosis drugs and prednisone for an eight to 12 month period. Twenty-two controls were followed simultaneously. These were not terminal but so-called "good chronics." Complete studies were done prior, during and after therapy. Severay untoward effects were noted, primarily diabetes in three patients

and cardiac decompensation in four others. No significant roentgen deterioration was observed. Ventilatory function studies were moderately to markedly improved. One unexpected and intriguing finding was the complete absence of hemoptysis in the prednisone treated group of which 10 had history of repeated hemoptysis.

RESUMEN

Se trataron 22 enfermos de tuberculosis pulmonar crónica activa con enfisema, mediante las drogas antituberculosas y Prednisona por un término de 8 a doce meses. Se observaron simultáneamente 22 testigos. Estos no eran casos terminales sino de los llamados "buenos crónicos." Se hicieron estudios completos antes, durante y después del tratamiento. Varios efectos dañosos se observaron consistentes en diabetes en tres enfermos y descompensación cardiaca en otros cuatro. No hubo deterioro visible a los rayos X. La función ventilatoria mejoró moderada o marcadamente. Un hallazgo inesperado y que causó perplejidad fué la ausencia completa de hemoptisis en los tratados con prednisona, diez de los cuales tenían antecedentes de repetidas hemoptisis.

RESUME

Un groupe de 22 malades atteints de tuberculose pulmonaire chronique, active, avec emphysème, fut traité par les médications antituberculeuses et la "Prednisone" pendant une période de 8 à 12 mois. 22 malades témoins furent suivis en même temps. Ceux-ci n'étaient pas des malades stabilisés, mais de soi-disant "bons chroniques." Des études complètes furent faites avant, pendant et après le traitement. De graves intolérances furent d'abord notées chez trois malades qui eurent du diabète, et chez quatre autres chez lesquels on constata une décompensation cardiaque. Aucune perturbation radiologique importante ne fut observée. Des études de la fonction respiratoire furent améliorées d'une façon modérée ou nette. Une constatation inattendue et intrigante fut l'absence complète d'hémoptysie dans le groupe traité á la Prednisone, dans lequel 10 malades avaient des antécédents d'hémoptysies répétées.

ZUSAMMENFASSUNG

Eine Gruppe von 22 Patienten mit chronischer aktiver Lungentuberkulose mit Emphysem wurden mit antituberkulösen Medikamenten und mit Pretnison 8-12 monatelang behandelt. 22 Kontrollen wurden gleichzeitig beobachtet. Hierbei handelte es sich nicht um therminale, sondern um sogenannte "gutartigchronische" Fälle. Vor, während und nach beendeter Therapie erfolgte eine komplette Durchuntersuchung. Einige ungünstige Wirkungen wurden in erster Linie bei Diabetis an 3 Kranken festgestellt und kardiale Dekompensation bei vier anderen. Es wurden keine erheblichen röntgenologischen Verschlechterungen bemerkt. Atemfunktionsproben zeigten eine mässige bis ausgesprochene Besserung. Ein unerwarteter und interessanter Befund war das vollständige Fehlen von Haemoptysen bei der mit Pretnison behandelten Gruppe, unter der sich 10 Fälle befanden mit einer Vorgeschichte von wiederholten Haemoptysen.

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The Role of Bronchography in the Diagnosis of Bronchogenic Carcinoma

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The resectability and five-year survival rate for bronchogenic carcinoma have not shown the anticipated rise in spite of a widespread awareness of the problem, broader application of roentgenographic survey of the general and selected population groups and the utilization of diagnostic exfoliative cytology. Evaluation of 300 patients admitted to the University Hospital prior to 1952 in whom the diagnosis of bronchogenic carcinoma was established demonstrated that the interval of time between the onset of symptoms of bronchogenic carcinoma and the first consultation with a physician averaged 11 weeks. In most of these patients an additional 22 weeks under medical observation and symptomatic treatment elapsed before definitive diagnostic studies and treatment were performed at this medical center. A more recent survey of this problem indicates a definite improvement in this costly delay, yet the deferral of definitive diagnosis and surgical therapy still persists and reflects the inherent difficulty in the present methods of early diagnosis of bronchogenic carcinoma.

The presence of bronchogenic carcinoma can be suspected on the basis of symptomatology, physical examination and plain roentgenograms; however, various nonmalignant pulmonary lesions may also produce these findings. Differential diagnostic procedures necessary to arrive at a final and accurate diagnosis are time-consuming, quite expensive, and frequently not successful. As a result, many physicians will persist in watching a lesion on serial x-ray films over a period of many months and years and apply the entire gamut of antibiotics. Repeated examination of bronchial secretions for malignant and endoscopy are resorted to. The first two methods certainly must be condemned. Cytological examination of bronchial secretions can be performed in a few centers by experienced pathologists. However, when such an individual is not available, these techniques become woefully inadequate and can be misleading. Because of its limitation of direct visual examination of only a portion of the tracheobronchial tree, bronchoscopy is diagnostic in less than half of all our patients with bronchogenic carcinoma and is particularly inadequate when dealing with lesions located in the periphery of the lung.

An aid in the diagnosis of bronchogenic carcinoma is bronchography. Contrast study of the bronchial tree has been available since 1922, and was shown to be of value in the diagnosis of bronchogenic carcinoma by Graham, Singer and Ballon[1] and others.[2-5] This procedure, used extensively in the investigation of bronchiectasis, lung abscess, tuberculosis and other pulmonary lesions, has not been used extensively in this country

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as an aid in the early diagnosis of bronchogenic carcinoma, although its value has been stressed in the foreign literature.[6-8] In 1952 bronchography was initiated as a standard procedure performed by members of the Department of Radiology at this medical center. A technique was adapted which allows fluoroscopic visualization of the entire tracheobronchial tree. As with examination of the gastrointestinal tract, spot films are used to record any persistent abnormality observed. In this manner the bronchi adjacent to a persistent density on plain x-ray film can be explored thoroughly and the presence or absence of a characteristic bronchial abnormality or block produced by carcinoma demonstrated.

This abnormality simply consists of a blocked bronchus, either main bronchus, segmental bronchus or subsegmental bronchus. Usually the cutoff is abrupt, especially in the lumen of smaller size. However, in the main bronchus or bronchus intermedius a tapered block may occur. The *persistent bronchial block* of a carcinoma is opposed to the distorted but still patent bronchial pattern of an infectious process. This difference has proved to be of utmost value in the differential diagnosis of bronchogenic carcinoma and infectious processes.

Methods and Results

To evaluate the usefulness and accuracy of bronchography in the differential diagnosis of bronchogenic carcinoma, the hospital records, roentgenograms and bronchograms of 1408 patients with various pulmonary lesions subjected to bronchography between January 1952 and December 1955 were reviewed (Table I). A clinical diagnosis of carcinoma of the lung was made in 259 of these patients, with histologic proof available in 236. The latter group forms the basis of this study. Although an additional 134 patients with proved bronchogenic carcinoma were admitted to the hospital during the same four-year period, bronchography was not performed and they have not been included in this evaluation.

The technique of bronchography has become a well-standardized procedure in the Department of Radiology of the Health Center. Following

TABLE I
THE FINAL DIAGNOSIS IN 1408 PATIENTS INVESTIGATED BY BRONCHOGRAPHY

Diagnosis	No. of Patients
Bronchiectasis	263
Bronchogenic carcinoma	259
Bronchitis	184
Pneumonitis	111
Emphysema	108
Tuberculosis	87
No bronchopulmonary disease	63
Bronchial asthma	43
Pleural lesions	37
Heart disease	27
Lung abscess	22
Metastatic carcinoma	19
Mediastinal tumors	12
Miscellaneous	173

a review of the patient's clinical record and plain roentgenograms, the procedure is performed by the radiologist. The bronchography is carried out in the early afternoon and nothing is allowed by mouth on the day of the procedure except a light breakfast. Fifty mgm. of seconal® is given 30 minutes prior to the procedure. Anesthesia of the nose, nasopharynx, oropharynx, larynx and tracheobronchial tree is accomplished by local application of 2 per cent pontocaine® solution. A No. 14 French Coude catheter is passed either blindly or under fluoroscopic guidance through the nose into the trachea and secured by adhesive tape to the cheek when positioned just above the coryna. With the patient in the supine position on the tilting fluoroscopic table the contrast medium is introduced under visual control into the right or left bronchial tree by rotating the patient to either side. Ten cc. of lipiodol® or 10 to 15 cc. of dionosil® is usually sufficient to outline adequately one side of the tracheobronchial tree. With the demonstration of a bronchial block during the examination, repeated efforts are made to fill the involved bronchus by changing the position of the patient, instructing him to inhale deeply, or by instillation of additional contrast media until the examiner is satisfied that an actual obstruction is present and persists. Spot films are taken not only of the involved bronchus but also of the remainder of the tracheobronchial tree. Following this procedure the standard 14 x 17 inch vertical roentgenograms are made in the posteroanterior, oblique and lateral projections. In isolated instances stereoscopic and delayed roentgenograms are also used. If it is suspected that the bronchial block might be due to retained mucus or blood, the examination is repeated at a later date. In patients with severe hemoptysis an interval of several days is allowed prior to bronchography although hemoptysis of a lesser degree is no contraindication. Patients with profuse or tenacious sputum are treated with postural drainage, bronchodilators, wetting agents and antibiotics for several days prior to examination.

It has been generally assumed that surgery should not be performed for at least two weeks following bronchography. The opinion is prevalent that bronchography may produce febrile reaction due to pneumonitis or reduce pulmonary respiratory function. No evidence of bronchopulmonary infection following the instillation of lipiodol® has been observed in this series of cases. However, with instillation of dionosil®, febrile reaction occurred on several occasions on the day of bronchography and persisted for several days.

Respiratory function studies were performed in a group of patients pre- and post-bronchography and 24 hours later. There was no appreciable decrease in maximum breathing capacity in these patients and in some an increase in ventilation followed the bronchography.

Bronchoscopy was performed in the majority of patients undergoing bronchography. Although early in this study bronchoscopy was done first, this procedure is now performed following the bronchography. After demonstration of a bronchial block by contrast media the endoscopic examination is accomplished with greater facility since the exact location of the bronchial lesion is known. Special endoscopic examination can be performed, particularly if the lesion has been localized in an inaccessible upper lobe bronchus. Also, bronchoscopy may initiate hemoptysis and

TABLE II
ROENTGENOGRAPHIC AND BRONCHOGRAPHIC FINDINGS IN 236 PATIENTS WITH PROVED BRONCHOGENIC CARCINOMA

Plain Roentgenograms	No. of Patients	Bronchial Block	
		Present	Absent
Circumscribed mass	69	56	13
Infiltration	57	55	2
Atelectasis	56	56	0
Hilar or mediastinal mass	40	30	10
Pleural effusion	13	13	0
Abscess	1	0	1
TOTAL	236	210	26
	100 per cent	89 per cent	11 per cent

produce mucosal edema, resulting in a transient bronchial abnormality. For these reasons bronchoscopy is delayed until the completion of the bronchogram.

All of the 236 patients with bronchogenic carcinoma demonstrated various types of intrathoracic densities on plain roentgenograms (Table II). In 69 patients the lesion was described as a circumscribed mass, not contiguous with the mediastinum, hilar structures, chest wall or diaphragm. A bronchial block was present in 56 (80 per cent) of these patients. Since circumscribed masses within the lung parenchyma are considered usually to be surgical lesions, bronchography and bronchoscopy in such patients are not necessarily indicated. However, bronchography more frequently than bronchoscopy and exfoliative cytology gives positive information by demonstrating the typical bronchial block.

In 57 patients the lesion was described as infiltrative, radiating from the hilum yet located totally within the lung parenchyma, resembling the pattern of pneumonitis. It was in this group of patients that the bronchogram proved of greatest value in that the bronchial block was demonstrated in 97 per cent of the patients with bronchogenic carcinoma.

The radiologist reported atelectasis in 56 patients and intrabronchial occlusion was demonstrated in all. In 40 patients with hilar or mediastinal masses the bronchogram showed obstruction in only 75 per cent. Pleural effusion, which may mask underlying atelectasis and parenchymal lesions, was found in 13 patients. In all of these cases the bronchial occlusions was clearly established by bronchography. There was one patient who on plain x-ray examination demonstrated a lesion typical of a lung abscess.

TABLE III
BRONCHOGRAPHIC FINDINGS AND CELL TYPE OF BRONCHOGENIC CARCINOMA

Cell Type	No. of Patients	Bronchial Block	
		Present	Absent
Squamous	151	132	19
Undifferentiated	68	62	6
Adenocarcinoma	11	10	1
Alveolar	6	6	0
TOTAL	236	210	26

TABLE IV
LOCATION OF BRONCHIAL BLOCK IN 210 CASES OF BRONCHOGENIC CARCINOMA AND ITS RELATION TO RESECTABILITY

Location of Block	No. of Patients	Resected	
		No. of Patients	Per Cent
Main bronchus	46	16	35
Lobar bronchus	114	46	40
Segmental bronchus	50	27	55
TOTAL	210	89	43

The bronchogram did not demonstrate bronchial block or irregularity but at operation carcinoma was found.

In the 236 patients with pulmonary malignancy the cell type (Table III) was squamous in 151, undifferentiated in 68, adenocarcinoma in 11, and alveolar-cell carcinoma in 6. Bronchial block was found in 87 per cent of the patients with squamous-cell carcinoma, 92 per cent of those with undifferentiated carcinoma, 91 per cent of those with adenocarcinoma and 100 per cent of those with alveolar-cell carcinoma.

The site of the bronchial block in the 210 patients with proved pulmonary malignancy was in the main bronchus in 46 (22 per cent) patients; in the lobar bronchus in 114 (54 per cent); and in a segmental bronchus in 40 (24 per cent) (Table IV). Resection was accomplished in 16 (35 per cent), of the 46 patients with bronchographic evidence of obstruction of the main bronchus; 46 (40 per cent) of 114 patients with lobar bronchial obstruction; and 27 (54 per cent) of 50 patients with segmental block. The resectability rate for the 210 patients in whom bronchial block was demonstrated by bronchography was 42 per cent, while in the 26 without demonstrable bronchial abnormality it fell to 34.6 per cent.

Bronchoscopy was performed in 152 of the 210 patients showing a bronchial block on bronchography (Table V). The diagnosis of carcinoma of the lung was established by bronchial biopsy in 29 and by cytology in four, (77 per cent) of the 43 patients with involvement of the main bronchus. Of the 73 with a lobar block, 45 per cent had the diagnosis established, 25 by a positive bronchial biopsy and eight by positive cytology. Only 12, (33 per cent) of the 36 patients with segmental block had the diagnosis made by endoscopy. Seven had positive biopsy and five had positive cytology. In a total of 163 with or without bronchial block

TABLE V
THE RESULTS OF BRONCHOSCOPIC EXAMINATION IN PATIENTS WITH BRONCHIAL BLOCK

Location of Block	No. of Patients Bronchoscoped	Diagnosis Established	
		No. of Patients	Per Cent
Main bronchus	43	33	77
Lobar bronchus	73	33	45
Segmental bronchus	36	12	33
TOTAL	152	78	51

due to bronchogenic carcinoma, bronchoscopy established the diagnosis in only 80 cases, (49 per cent) by direct biopsy or cytological examination of the aspirated bronchial secretions.

DISCUSSION

To be of diagnostic value in a patient suspected of having bronchogenic carcinoma, bronchography must be performed meticulously under fluoroscopic control. Every effort must be made to fill each division of the bronchial tree. Should a bronchial obstruction be encountered, repeated efforts must be made to fill this area. Only when this is done can a bronchial obstruction be considered to be diagnostic of bronchogenic carcinoma.

All the patients with bronchial block do not have bronchogenic carcinoma. In those with nonmalignant disease the cause of the obstruction can readily be established by history, various x-ray techniques, and the character of the block. The bronchial block seen in bronchogenic carcinoma is usually a complete obstruction of the involved bronchus. When the block is not complete, there is mucosal irregularity proximal to, and in some instances distal to the block, suggesting the possibility of mucosal or submucosal extension of the tumor. Peribronchial lymph node metastasis occasionally is evidenced by convex deformity of the bronchial lumen.

During the four-year period covered by this study, 1408 patients were subjected to bronchography for various reasons. Bronchial block considered diagnostic of bronchogenic carcinoma was demonstrated in 213 cases. The diagnosis was confirmed in all but three patients of this latter group. Actinomycosis, cholesterol pneumonia and chronic interstitial pneumonitis were found in these cases.

Of the 236 patients proved to have carcinoma who underwent bronchography, 26 had normal bronchograms. The lesions in these 26 patients were described as parenchymal masses or nodules, hilar or mediastinal masses, infiltrations or abscess. While it is easily recognized why a peripheral lesion might not produce a visible bronchial block by virtue of the distal portion of the tracheobronchial tree involved, it is difficult to understand why masses near the hilus do not produce a characteristic bronchial block in a higher percentage of cases. The explanation can be offered that these tumors spread rapidly to the parenchyma of the lung or the adjacent lymph nodes with minimal involvement of the bronchus of origin. It is of interest that none of the 10 patients with a hilar or mediastinal mass and a normal bronchogram could be resected. This is in contrast to a resectability rate of 42.4 in those with bronchial obstruction.

The cell type of the tumor (Table III) *per se* bore no relation to the presence or absence of a bronchial block. The majority of patients had squamous-cell carcinomas, fewer had undifferentiated carcinomas and only a small group had adenocarcinoma. All of the six patients with alveolar-cell carcinoma had a bronchial block.

The bronchial block occurred in the main bronchus in about one-fifth, in a lobar bronchus in slightly over one-half and in the segmental bronchus in approximately one-quarter of the patients. Bronchoscopy was most effective in establishing the diagnosis in patients with bronchial obstruction in the main bronchus. In less than half of the patients with a lesion in the lobar bronchus and in one-third of those with a neoplasm of a segmental bronchus was bronchoscopy of diagnostic value. This supports the observation that in the more peripheral lesions the diagnosis of malignancy is difficult to establish by bronchoscopy. The usefulness of bronchography becomes apparent since 54 per cent of the patients with carcinoma in a segmental bronchus had the lesion resected, while in only 35 per cent of those with involvement of a main bronchus could the lesion be resected.

The high incidence of neoplasms in the presence of bronchial block in these patients would suggest that any patient in the carcinoma age group with an acute or chronic pulmonary lesion demonstrated by roentgenography who does not respond to specific therapy within a period of several weeks should be investigated by bronchography. If the area of "unresolved pneumonia" remains and bronchial block is absent by bronchography, the clinician may continue his care of this patient without too much concern about bronchogenic carcinoma. Obviously any patient with recurrent attacks of pneumonitis, despite a normal bronchogram on the first observation, should have this procedure repeated as part of the routine follow-up.

It has been suggested that an increased application of bronchography in the differentiation of pulmonary infiltrations may result in a high incidence of false positives and subsequent radical resection of nonmalignant lesions. This has not been the case in this series of 1408 patients in whom bronchograms were performed during a four-year period. There were only three patients with bronchographic evidence of bronchogenic carcinoma in whom the diagnosis was found at operation to be a nonmalignant lesion.

SUMMARY

In 1408 patients undergoing diagnostic bronchography for various pulmonary lesions during a four-year period, a bronchial block was demonstrated by this method in 210 of 236 cases of proved bronchogenic carcinoma, or an incidence of 89 per cent.

The diagnosis of bronchogenic carcinoma suggested by bronchography proved erroneous in only three cases of the entire series. This study indicates bronchography to be an additional and effective method for the diagnosis of bronchogenic carcinoma.

RESUMEN

En 1408 enfermos que se sujetaron a broncografía por varios padecimientos pulmonares durante 4 años se encontró un bloqueo bronquial en 210 de 236 de carcinoma bronquiogénico comprobado o sea en 89 por ciento.

El diagnóstico de carcinoma bronquiogénico sugerido por la broncografía sólo fué erróneo en tres casos de la serie.

Este estudio indica que la broncografía es un método adicional efectivo para el diagnóstico del carcinoma bronquiogénico.

RESUME

Sur 1408 malades subissant des bronchographies diagnostiques pour différentes lésions pulmonaires, pendant une période de 4 ans, on découvrit par cette méthode un arrêt bronchique chez 210 malades sur 236 atteints de carcinome bronchique prouvé, soit un taux de 89%.

Le diagnostic de carcinome bronchique, évoqué par la bronchographie se trouva erronné dans trois cas seulement sur la série complète. Cette étude indique que la bronchographie est une méthode supplémentaire et efficace pour le diagnostic du cancer bronchique.

ZUSAMMENFASSUNG

Unter 1408 Patienten, die während eines Zeitraumes von 4 Jahren wegen verschiedenartiger pulmonaler Veränderungen einer diagnostischen Bronchografie unterzogen wurden, wurde mit dieser Methode ein Bronchusverschluss in 210 von 236 Fällen von nachgewiesenem bronchogenem Carzinom demonstriert, d.h. eine Häufigkeit von 89%.

Die durch die Bronchografie nahegelegte Diagnose eines bronchogenen Carzinomas erwies sich als irrtümlich nur in 3 Fällen der ganzen Serie. Diese Untersuchung zeigt an, dass die Bronchografie ein zusätzliche und wirksame Methode für die Diagnose des Bronchuscarzinoms ist.

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Clinical Experience with Oxamycin

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This broad spectrum antibiotic, developed independently in two separate laboratories and introduced to clinical medicine under the names of oxamycin and cycloserine, was first used in the treatment of tuberculosis by Epstein et al. (1955) (1956). Further studies have been carried out by a Co-operative Veterans Administration—Army—Navy group (1955) and by Lester et al. (1956) and Renzetti et al. (1956).

A supply of this drug for clinical trial at the Mountain Sanatorium was obtained in November, 1955, through the courtesy of Merck Laboratories.

In view of the known toxic properties of oxamycin and the established value and safety of the currently available chemotherapeutic agents it was decided to confine the trial to cases previously treated unsuccessfully and the following suggested criteria for inclusion were drawn up:

(1) Previous chemotherapy for at least a year with the commonly used anti-tuberculosis drugs.

(2) Evidence of persisting cavitation.

(3) Persistently positive sputum cultures.

Cases of epilepsy or active serious mental illness were excluded. Thirty-four cases conforming to all three criteria were chosen and a further seven cases whose sputum cultures were negative but who had gross persisting cavitation were also included making a total of 41. It will be seen that these cases constituted an unfavourable group with an inherently bad prognosis.

It follows from the criteria of inclusion that bacterial resistance to the commonly used drugs would be expected. In fact, of 32 cases tested 17 were completely or partially resistant to streptomycin, PAS and isoniazid, 11 showed varying degrees of resistance to one or more of the three and four were sensitive to all three.

A six-month period of treatment was commenced on December 1, 1955, using oxamycin alone in a dosage of 500 mgms. daily given in two equally divided doses. As there became reason to believe that the initial dose of oxamycin used was somewhat low this was increased on March 1, 1956, to 750 mgms. daily given in three equal doses at eight-hourly intervals, and 300 mgms. of isoniazid was also added (irrespective of isoniazid resistance).

Progress During Trial

Of 41 cases entering the trial, 28 completed the initial six-month period. The reasons for abandoning treatment (13 cases) are seen in Table I.

A. Clinical Progress

Weight gain varying from 2 to 16 pounds (mean gain 6.5 pounds) occurred in 27 of 28 cases completing trial. Appreciable weight loss was noted in only one case who lost nine pounds.

Considerable improvement in general condition occurred in six cases and clinical worsening in only one whose treatment was therefore changed.

TABLE I

TREATMENT WITHDRAWALS (13 CASES)	
Toxic symptoms	7
Change of treatment	3
Death	1
A.W.O.L.	1
Drug refused	1

Three already on the borderline of respiratory insufficiency continued a downhill course and died.

Healing of skin sinuses occurred in two cases of broncho-pleural fistula and empyema.

B. Sputum Studies

As in previously recorded series conversion of smears to negative was a frequent finding and often persisted to the end of the trial.

Conversion of sputum cultures to negative occurred in seven of 22 sputum positive cases who completed trial. One further case whose treatment was discontinued at four months also converted and remains negative to date. Cultures from one of seven cases originally sputum negative became positive in April, 1956, and subsequently.

The timing of sputum conversion from the start of the trial in December, 1955, is seen in Table II.

It will be seen that conversion tended to occur early in cases likely to respond favourably.

Radiological Changes

These were assessed by monthly x-ray films and three-monthly tomographs. As might be expected in a group of this nature, little radiological change was noted. Almost all were cases of far advanced chronic cavitary disease and although some fluctuation in cavity size occurred in a few cases, no constant pattern was noted. The findings of note were as follows:

1. Cavities persisted in all cases which underwent sputum conversion and in only one was appreciable reduction in cavity size noted.

2. Two further cases remaining sputum positive showed appreciable reduction in cavity size.

3. Increased shadowing occurring in one was shown at autopsy to be due to complicating bronchogenic carcinoma.

TABLE II
SPUTUM CULTURE REPORTS

Case No.	Nov.	Jan.	Feb.	Mar.	Apr.	May	June
1	+	—	—	—	—	—	—
2	+	—	—	—	—	—	—
3	+	—	—	—	—	—	—
4	+	+	—	—	—	—	—
5	+	+	+	—	—	—	—
6	+	+	+	+	—	—	—
7	+	+	+	+	+	+	—

4. Radiological evidence of spread of disease was noted in only one case, occurring three months after oxamycin was discontinued.

Toxic Symptoms

Their nature, frequency and timing are seen in Table III.

It will be seen that all were related to the central nervous system. Both cases of mental confusion were arteriosclerotic elderly men who had shown minor mental aberrations prior to treatment. Confusion persisted after drug was withdrawn in both and may well have been due to degenerative cerebro-vascular disease. Two who had previously undergone a period of mental hospital treatment for psychosis completed the six-month course without showing deterioration.

In spite of the increased oxamycin dosage in the second three months, only three cases developed toxic symptoms during this period, possibly in part due to equal spacing of doses throughout 24 hours.

No significant abnormality was revealed in course of regular blood counts, urinalyses and tests of kidney and liver function.

Progress Report On Cases Which Underwent Sputum Conversion

A review in June, 1957, 12 months following completion of the initial six-month treatment period included information on all eight cases. Oxamycin had been stopped at the end of the six month trial in three and after eight months in one. Three were still on the drug. As previously mentioned one case had stopped treatment at four months. All cases were clinically well with little or no cough and sputum. Sputum cultures or laryngeal swabs had remained consistently negative. Six of the eight had been discharged. Little or no radiological change had occurred.

Discussion

Oxamycin appears to be a useful addition to the therapeutic armamentarium in those cases failing to respond to the usual regimes. Its success in achieving sputum conversion in eight of 21 cases seems all the more worthy when viewed in the light of their previous failure to respond to treatment. It may be significant that bacteriological cure and closure of sinuses was achieved in two cases of post-operative broncho-pleural fistula and empyema as these cases are notoriously difficult to cure by other means.

Toxic symptoms are likely to restrict the use of the drug to cases not responding favourably to the commonly used drug combinations, although it may be possible to minimize these by the careful spacing of doses. Given with the relatively small dose used in this series treatment was discontinued in seven cases because of toxic symptoms.

TABLE III
NATURE AND TIME OF ONSET OF TOXIC SYMPTOMS

Symptoms	1st month	2nd month	3rd month	4th month	5th month	6th month	TOTAL	Treatment Stopped
Convulsion	2	—	—	1	—	—	3	2
Dizziness	3	—	1	1	—	—	5	2
Nervousness and Excitability	—	—	1	—	—	—	1	1
Confusion	—	1	1	—	—	—	2	2
TOTAL	5	1	3	2	—	—	11	7

It has recently been suggested by Barclay et al. (1957) that the combination of the drug with phenobarbitone or dilantin will appreciably reduce the incidence of neurotoxicity.

Considerable radiological improvement cannot be hoped for in these far advanced cases. A much longer period of observation will be necessary before the possibility of open cavitary healing in this group can be considered.

Experience with other chemotherapeutic agents would suggest a minimum treatment period of 12 months in this group. It is noteworthy, however, that three cases treated for six months and one for four months remain well and sputum negative 12 months after termination of treatment.

SUMMARY

A clinical trial of oxamycin in a group of 41 cases of far advanced pulmonary tuberculosis previously treated unsuccessfully resulted in sputum conversion in eight of 21 cases who received adequate treatment.

A review of the successfully treated cases 12 months after completion of the original treatment period revealed that all were well with stable x-ray film shadows and negative sputum cultures.

RESUMEN

En un grupo de 41 casos de tuberculosis pulmonar muy avanzada antes tratado sin éxito, se logró la negativación de esputos en 8 de los 21 que recibieron el tratamiento adecuado.

La revisión de los casos tratados, doce meses después, de terminado el tratamiento, demostró que todos estaban bien con aspecto radiográfico estable y cultivos de esputos negativos.

RESUME

L'auteur rapporte un essai clinique de traitement par l'oxamycine, dans un groupe de 41 malades atteints de tuberculose pulmonaire très grave, qui avait été antérieurement traités sans succès. On observa la négativation des crachats sur 8 des 21 cas qui furent convenablement traités.

En revoyant les malades traités avec succès douze mois après la cessation du traitement, on constata que tous étaient en bonne santé, evec des ombres radiologiques stables, et des cultures d'expectoration négatives.

ZUSAMMENFASSUNG

Eine klinische Versuchsreihe mit Oxamycin an einer Gruppe von 41 Fällen mit weit fortgeschrittener Lungentuberkulose, die zuvor vergeblich behandelt worden war, ergab Bazillenfreiheit im Auswurf bei 8 von 21 Fällen, die eine adäquate Behandlung erhalten hatten.

Eine Überprüfung der erfolgreich behandelten Fälle 12 Monate nach Abachluss der ursprünglichen Behandlungsperiode ergab, dass sie alle in Ordnung waren mit konstanten Röntgenaufnahme-Befunden und negativen Sputum-Kulturen.

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Intracavitary and Intrabronchial Fungus Masses*

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KAREL P. van de WOESTIJNE, M.D. and ANDRIES GYSELEN, M.D.
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In 1938 Dévé described a hitherto unreported form of aspergillosis of the lung, the megamycetoma, later also named aspergilloma[4] or intracavitary fungus ball[3].

This anatomo-radiological entity consists of a mass of mycelium filaments lying loose in a cavity in the lung and separated from the wall by a characteristic layer of air which is easily visible on radiography.

Recently we observed two interesting cases of mycosis of the lung: the first, a typical aspergilloma, but unusual because of its bilateral localization; the second, an endobronchial form of the disease, in which the whole left bronchial tree was filled with a mass of fungus identical with that found in an aspergilloma.

Case 1: This 52 year old man was admitted to the department of chest diseases on November 18, 1955, with haemoptysis and recurrent bloody sputum for one week.

In 1947, on a routine fluoroscopic examination, he was found to have some "opacity" in the apices of both lungs. Although no x-ray film was made at that time, it was thought to be an old and stabilised tuberculous lesion.

Up to 1951 he had no bronchopulmonary complaint. He then developed cough and had blood-stained purulent sputum, but little fever. Tuberculostatic treatment was instituted for one month; he thereafter felt improved and resumed his occupation.

In 1954 he was admitted elsewhere for recurrence of bloody sputum. There was no fever and repeated examination of the sputum, both by direct and culture methods, failed to demonstrate tubercle bacilli.

At that time x-ray films of the lungs showed lesions identical with those observed when he was admitted to the hospital 15 months later. Despite the absence of acid-fast bacilli, he again was treated by tuberculostatics and rest.

Besides these bronchopulmonary symptoms, he gave a history of pain and stiffness in the back, shoulders and hips of 25 years duration, due to rheumatoid spondylitis.

On November 18, 1955, he was admitted to the department of lung diseases at Louvain, because of a new grave haemoptysis. On admission he did not appear acutely ill. The haemoptysis had ceased and there was no fever. Over the apex of the left lung anteriorly, there was dulness on percussion, and auscultation revealed bronchial breathing. X-ray films and planigrams showed a circular shadow with a small clear zone surrounding it, localised in the left apex (Figure 1). One identical but smaller lesion was noted in the right apex (Figure 2). From these radiological appearances a tentative diagnosis of bilateral aspergilloma was made.

Subsequent cultures of sputum and of a puncture biopsy of the left mass gave an abundant growth of a fungus which was identified as aspergillus fumigatus. Tubercle bacilli were never found. Operation was avoided on account of the bilateral localization of the disease and the accompanying spondylo-arthritis.

Case 2: This 53 year old woman was admitted on April 25, 1955, because of cough productive of copious purulent sputum and recurrent haemoptysis. She had enjoyed good health until September 1946, when she gradually developed cough and purulent expectoration. Acid-fast bacilli were not found in the sputum at that time. X-ray films showed atelectasis of the entire left lung clearing rapidly after treatment with penicilline, but leaving a patchy infiltration over the whole left lung.

She continued to have some cough and in 1948 atelectasis of the left upper lobe was noted. She refused treatment, as she had but minor complaints.

In September, 1954 a new period of cough and purulent sputum ensued which grew progressively worse. On two occasions she had haemoptysis. Again tubercle bacilli were not found in the sputum.

X-ray films in January, 1955 showed a destroyed left lung with opacification of the whole parenchyma and diffuse bronchiectasis. In the apex a giant thin-walled cavity was noted.

She was admitted to the department of chest diseases at Louvain on April, 1955, complaining of cough and copious purulent sputum. She had lost weight but otherwise appeared fairly well. Bronchial râles and impairment of the percussion note over the

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left lung were noticed. X-ray films and planigrams were identical with those of January, 1955. On bronchography the left main bronchus was seen to be irregularly stenosed; further on the whole bronchial tree showed enormous saccular and cystic bronchiectasis. In many of these cystic dilatations filling defects were noted (Figure 3).

Repeated examinations of the sputum failed to demonstrate acid-fast bacilli. The white blood count was normal and there was no eosinophilia.

As the right lung appeared normal, a left pleuro-pneumonectomy was performed on June, 1955. The postoperative course was uneventful and she made a good recovery.

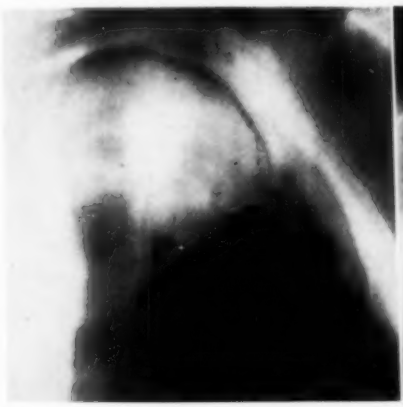

FIGURE 1

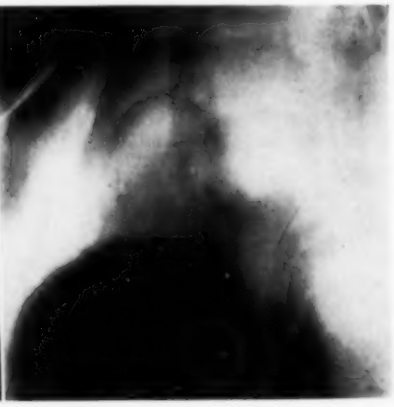

FIGURE 2

Figure 1 (Case 1): Planigram of the apex of the left lung showing a circular shadow surrounded by a small and characteristic clear zone.—*Figure 2* (Case 1): Planigram of the right apex showing an identical but smaller circular shadow also surrounded by a clear zone.

FIGURE 3 (Case 2): Bronchography on admission; in most cystic dilatations filling defects, due to intrabronchial fungus masses, are noted.

Pathology: The left lung was markedly collapsed, the main bronchus and the ascending branch of the upper lobe just before the bifurcation, were grossly stenosed. There was diffuse bronchiectasis and almost all the bronchi were filled with amorphous debris, brownish in the large bronchi and whitish in the bronchioli. This material was nowhere adherent to the wall and could easily be removed. In the apico-posterior segment was a cavity, about the size of a lemon, with a white smooth surface, and containing but little of the brownish material. On microscopic examination the bronchi were lined by ciliated columnar epithelium. Microscopy of the bronchial wall revealed ciliated columnar epithelium beneath which was found a considerable inflammatory exudate. Immediately under the epithelium this consisted chiefly of plasma cells but in the submucosa lymphocytes predominated.

The large bronchi were filled with a dense meshwork of interwoven mycelia interspersed with and separated from the bronchial wall by a layer of pus (Figs. 3 and 4). Eosinophils were not noted. In the bronchioli the mycelium was sparser, the whitish material consisting chiefly of pus. Nowhere in the bronchial walls, the lung parenchyma or the lymph nodes was evidence of tuberculosis found.

Mycology: The mycelial filaments are septate, belonging probably to the group of Fungi Imperfecti. Cultures were not made.

Discussion

In the classical form of mycosis of the lung, the fungus invades the tissues, producing bronchial lesions, mycotic granulomata or abscesses in the parenchyma. Two other types are also recognized: the intracavitary fungus ball (aspergilloma) and the allergic form. Our first case is a typical aspergilloma: the history of recurrent haemoptysis and blood-stained sputum never containing tubercle bacilli, the good general condition, together with the radiological appearances, were highly suggestive of this disease. An Aspergillus Fumigatus was found in the sputum both by direct microscopical examination and by culture. The final diagnosis was affirmed by culture of the same fungus from puncture of the mass in the left apex.

Although no puncture was done in the right mass, the same etiology may be assumed since the radiological appearances were identical. Such a bilateral localization, visible on x-ray films, is a great rarity.

The allergic type was first described in 1952 by Hinson, Moon and

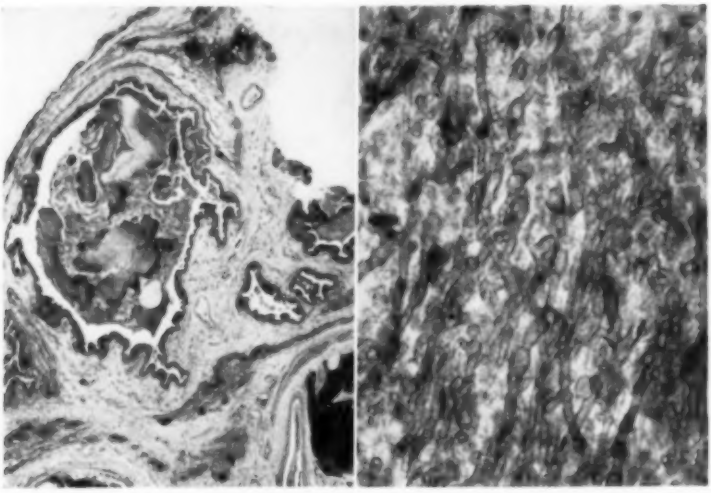

FIGURE 4 (Case 2): Low power view of intrabronchial mycelium masses interspersed with layers of pus nowhere adherent to the bronchial wall.—FIGURE 5 (Case 2): High power view of the mass of interwoven mycelium filaments.

Plummer.[3] It is characterized by recurrent collapse and consolidation in different parts of the lungs, caused by bronchial obstruction with typical "plugs." These plugs consist of sparse mycelium filaments aggregated together with mucus, fibrin, eosinophils, Curshman's spirals and Charcot-Leyden crystals, into rounded, brown, dull granular masses about one centimeter in diameter. The patients have asthmatic complaints and show blood eosinophilia.

The clinical course of our second case, especially the history of relapsing atelectasis, bears some resemblance to the description of Hinson, Moon and Plummer. However, in our case asthma and esinophilia were lacking. No plugs were ever coughed up, and the atelectases were always confined to the left lung, the right one remaining completely intact. Moreover, the anatomopathological findings were quite different; in contrast to the usual composition of the plugs, the mass that filled the whole bronchial tree of this lung chiefly consisted of a very dense network of hyphae, containing few other elements. This is the microscopic appearance of a true megamycetoma or intracavitary fungus ball. We therefore believe it is a special form of such a megamycetoma: an endobronchial fungus mass.

Bronchiectasis frequently develops beyond a bronchial stenosis of any etiology. In our second patient, the restriction of the fungus growth to the post-stenotic part of the bronchial tree, seems to indicate that the fungus developed in a bronchus already bronchiectatic, and the theory that the fungus itself was the primary cause of the bronchial dilatation ("l'aspergillome bronchiectasiant" of Monod) cannot be accepted here. The cause of the stenosis of the left main- and upper-lobe bronchus remains unknown and no specific lesion has been found in the serial sections of the stenosed bronchus.

SUMMARY

Two cases of mycosis of the lung are reported. The first a typical aspergilloma, but with bilateral localization; in the second case the same fungus mass as found in an aspergilloma was filling the whole left bronchial tree. It is believed to be an endobronchial form of the same disease.

RESUMEN

Se describen dos casos de micosis pulmonar. La primera es un aspergiloma típico pero de localización bilateral. En el segundo caso se encontró el total del árbol bronquial izquierdo llenado por la mismo masa fungosa que se encuentra en un aspergiloma. Se cree que se trata de una forma endobronquial de la mismo enfermedad.

RESUME

Les auteurs rapportent deux cas de mycose du poumon. La première est un aspergillome typique, toutefois à localisation bilatérale; dans le second cas, la même masse fongique que celle que l'on rencontre habituellement dans l'aspergillome remplissait la totalité de l'arbre bronchique gauche. Ils pensent qu'il s'agit d'une forme endobronchique de la même affection.

ZUSAMMENFASSUNG

Bericht über 2 Fälle von Mycose der Lungen.

Der erste ist ein typisches Aspergillom, jedoch mit bilateraler Lokalisation; bei dem zweiten Fall füllte die gleiche Pilzmasse, wie man sie bei einem Aspergillom findet, den ganzen linken Bronchialbaum aus. Es wird angenommen, dass es sich um eine endobronchiale Form der gleichen Erkrankung handelt.

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SECTION ON CARDIOVASCULAR DISEASES

The Pathologic Anatomy of Ventricular Septal Defects*

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Ventricular septal defects are best considered under two categories: 1) isolated ventricular septal defects, and 2) those associated with other abnormalities.

1. Isolated Ventricular Septal Defects (Fig. 1).[1-17] The isolated ventricular septal defect is usually situated beneath the aorta. Less commonly, but not rarely, it may be found in any other part of the muscular ventricular septum. Although usually single, defects may be multiple (Fig. 2). Those that are present beneath the aorta are often situated in the region of the pars membranacea, and the adjacent anterior portion of the muscular ventricular septum. Their upper margin may be separated from the base of the aorta by a small portion of pars membranacea or anterior ventricular septum. Where the upper margin of the defect is confluent with the mouth of the aorta, then the aorta may override (see Eisenmenger complex below). These defects open beneath the normally placed, or slightly deviated crista, at the junction of the sinus and conus of the right ventricle, adjacent to the anterior part of the medial leaflet of the tricuspid valve. Less commonly, a greater part of the anterior ventricular septum is involved, and uncommonly the defect is limited to the anterior part of the ventricular septum. The latter have been called "high" defects (Fig. 3). This appellation concerns itself with the position of the defect in the right ventricle, since these enter somewhere in the conus, within or even above the normally placed crista.

The terms anterior and posterior parts of the ventricular septum, or simply anterior and posterior ventricular septum, are spoken of in the embryologic, and not in the purely anatomic sense. The definitive ventricular septum may be considered to be divided into three parts, according to its embryologic origin (Fig. 4): 1) the posterior ventricular septum, as seen from the left side, consists of all of the anatomically posterior—and the entire apical portion of the definitive ventricular septum. As seen from the right side, it includes all of the septum posterior to the septal band of the crista, on the lower part of which runs the right

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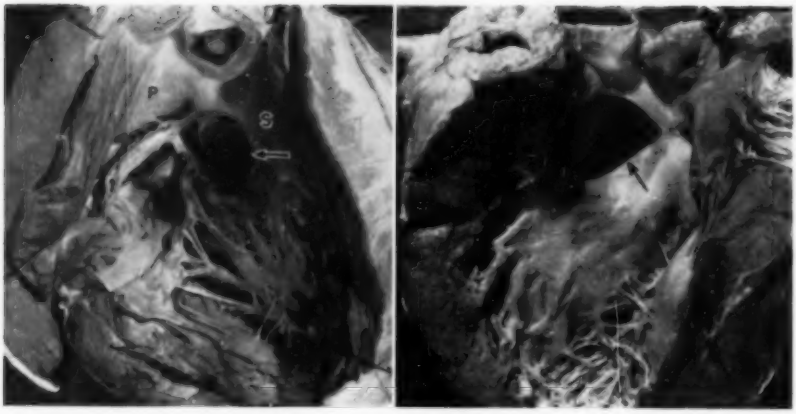

FIGURE 1A FIGURE 1B

Figure 1: Complex associated with large isolated ventricular septal defect. (A) Right ventricular view. (B) Left ventricular view. S—Septal band. P—Parietal band. Arrows point to the defect.

bundle branch. Strictly speaking, all of the septum posterior to the right bundle branch is the posterior septum[15]. This is the part which is derived from the original ventricular septum anlage of the embryo; 2) the anterior part of the muscular ventricular septum, as seen from the left side, consists of the anatomic anterobasal portion of the muscular ventricular septum from the base of the aorta to a point a varying distance distally. As seen from the right side, it consists of all the muscular septum anterior to, and including, the crista. Strictly speaking, all the septum anterior to the right and left bundle branches is the anterior septum. Thus, on the left side, the anterior part of the septum is relatively small as compared to the posterior, while on the right side it is relatively larger as compared

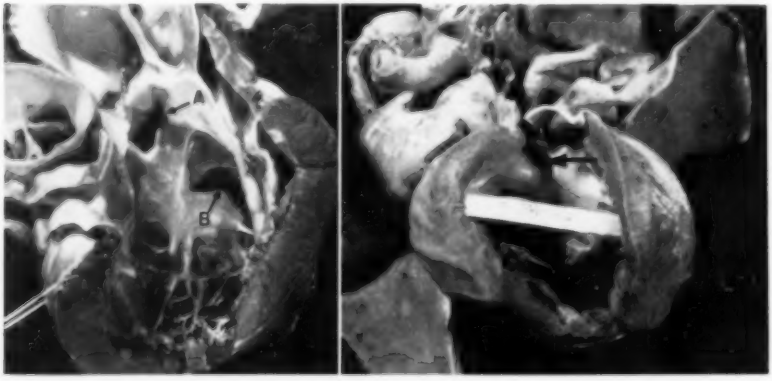

FIGURE 2 FIGURE 3

Figure 2: Multiple ventricular septal defects. Left ventricular view. A—Defect in the pars membranacea and the anterior ventricular septum. B—Defect in the posterior ventricular septum.—*Figure 3:* Isolated high ventricular septal defect. Right ventricular view. Arrow points to the defect.

to the posterior, but still smaller than the posterior septum. The difference in surface area of the anterior septum on both sides is related to the presence of the separate conus on the right side and the complete fusion of the conus on the left side. This part of the ventricular septum is derived from the bulbar septum of the embryo; 3) the pars membranacea lies directly adjacent to the base of the posterior part of the right anterior, and the anterior part of the posterior aortic cusp. Only part of the membranous septum is interventricular, a varying extent of it being right atrio—left ventricular. The membranous septum is derived from the endocardial cushions, with a varying participation of the proximal bulbar cushions, and the original anlage of the posterior ventricular septum.

However, the position of the defect is less important than its size[5]. Thus, in considering the pathologic complexes produced by ventricular

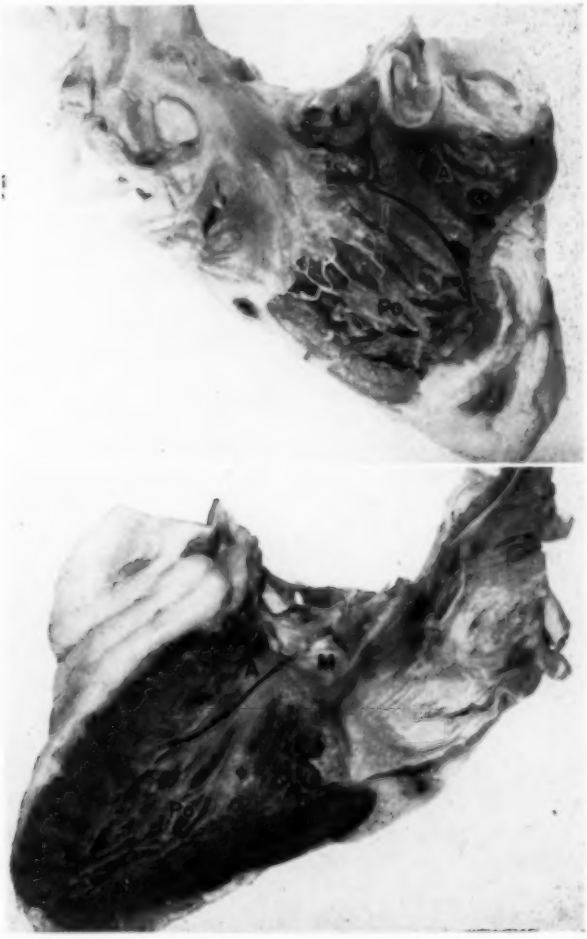

FIGURE 4A

FIGURE 4B

Figure 4: Topography of normal atrial and ventricular septa. (A) Right sided view. (B) Left sided view. A—Anterior septum. Po—Posterior septum. M—Membranous septum. Dark line demarcates the division zone between anterior and posterior septa.

septal defects, it is best to divide them into those associated with small and large defects.

A. Small defects (Fig. 5). These defects are associated with small left to right shunts, which are insufficient to produce hypertrophy of either the right or left ventricle. They are thus innocuous of themselves, but their complications may be serious, as described below. Rarely, a small defect may secondarily close, as in a case seen by this author in the specimen collection of Dr. Otto Saphir.

B. Large defects (Figs. 1-3). These are defects which produce sufficient shunt as to be hemodynamically important. Here the right ventricle, as seen at autopsy, is always hypertrophied, and occasionally equals or exceeds the thickness of the left ventricle. The left ventricle is sometimes hypertrophied, and sometimes not. There is not always correlation between the electrocardiographic interpretation of left ventricular hypertrophy and the findings at autopsy. The left atrium is usually large. The pulmonary artery is dilated, and sclerotic changes may be noted in the main pulmonary trunk, where pulmonary hypertension is known to exist by catheterization. Hemodynamic sclerotic changes may also be noted in the tricuspid and pulmonic valves and increased fibroelastosis in the left atrium. Fibroelastosis may also be noted in the margins of the defect, and focally in the endocardium of the conus. The complications of ventricular septal defects are: a) subacute bacterial endocarditis may be engrafted on the defect; b) hemodynamic changes at the defect may exert a pull on the aortic valve with herniation or deformity to produce aortic insufficiency; c) the bundle of His may be involved in secondary fibrosis and disruption in continuity to produce partial or complete heart block; and d) the medial leaflet of the tricuspid may become adherent to the defect to produce tricuspid insufficiency.

It should be reemphasized, what was pointed out by Mönckeberg[19-21]

FIGURE 5

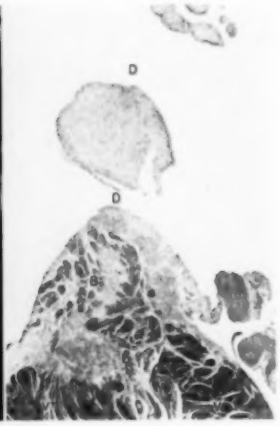

FIGURE 6

Figure 5: Small isolated defect of the ventricular septum. Left ventricular view. Arrow points to the defect.—*Figure 6:* Section through the ventricular septum in the region of the defect showing the bundle of His with considerable fibrosis. Hematoxylin-eosin stain. × 47. B—Bundle of His. D—Defect. V—Ventricular septum.

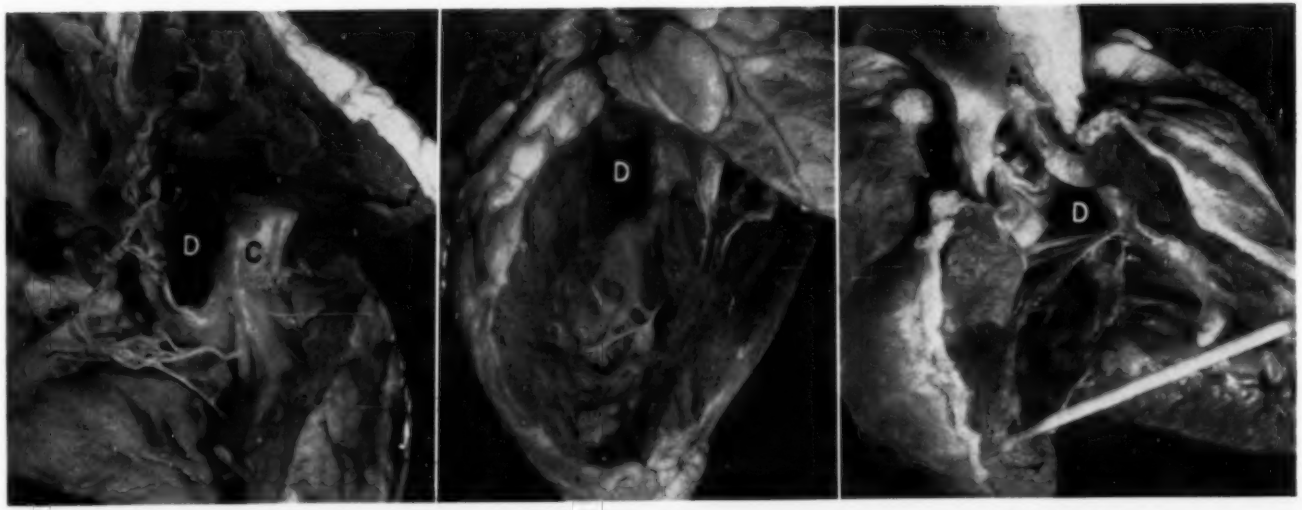

FIGURE 7A FIGURE 7B FIGURE 7C

Figure 7: The ventricular septal defect in tetralogy of Fallot. (A) Right ventricular view looking into the conus, showing the relationship of the defect to the deviated crista. (B) Left ventricular view. (C) Right ventricular view showing relationship of the defect to the aorta. D—Defect. C—Crista. A—Aorta.

and Keith[22] and reiterated recently,[23] that the bundle of His lies on the posterior or inferior margin of the defect, where the defect lies in the subaortic area (Fig. 6).

2. Ventricular Septal Defects Associated with Other Abnormalities.

A. Tetralogy of Fallot (Fig. 7).[15-17, 24-33] The ventricular septal defect in tetralogy of Fallot is usually large. It is usually situated in the anterior ventricular septum beneath the aorta and includes the anterior part or all of the pars membranacea. Its upper margin is absent, the opening being

FIGURE 8

Figure 8: Topography of the normal crista. S—Septal band. P—Parietal band.—*Figure 9:* The defect of the ventricular septum in the Eisenmenger complex. A—Aorta. Arrow points to the defect.—*Figure 10:* The ventricular septal defect in partial transposition of the Fallot type (Double outlet right ventricle with decreased pulmonary flow). S—Septal band. P—Parietal band. A—Aorta. Arrow points to the defect.

FIGURE 9

FIGURE 10

confluent with that of the straddling aorta. It opens into the conus of the right ventricle beneath (posterior to) the deviated crista. The exact position of the defect in the right ventricle can be understood only by a knowledge of the normal muscle bundle architecture of the conus, and the deviation in architecture in overriding aorta complexes.

In 1937, Lev and Saphir[30] restudied the muscle bundles of the conus based on the previous work of Keith,[22, 27] Spitzer,[32] and Tandler.[34] From a study of normal and congenitally abnormal hearts, in contrast to other authors, they considered the entire arch of musculature guarding the entry into the conus as the crista supraventricularis (Fig. 8). This they

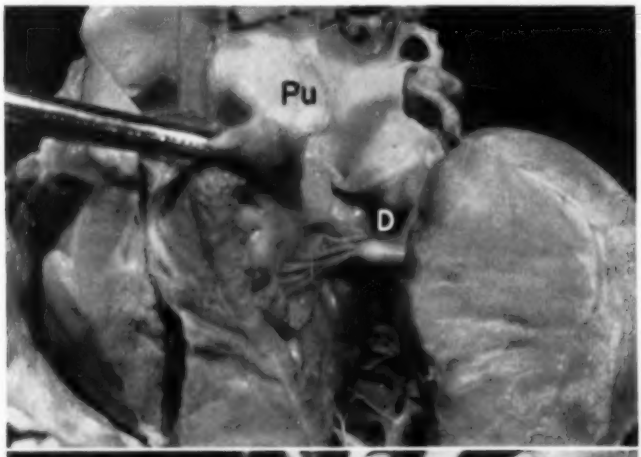

FIGURE 11A

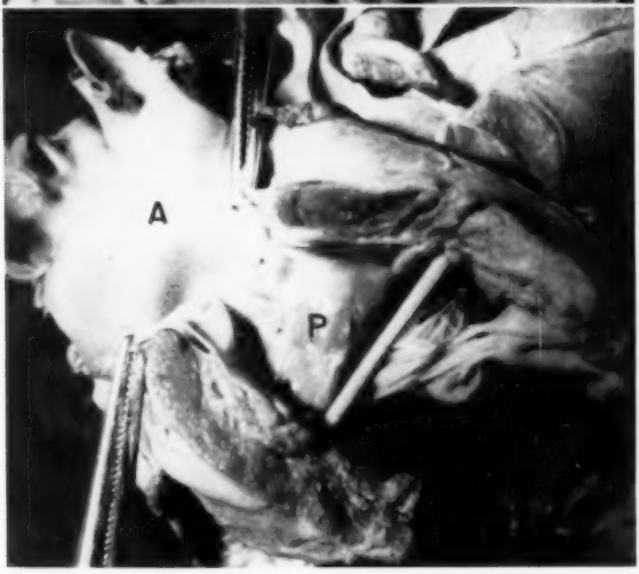

FIGURE 11B

Figure 11: The Taussig-Bing heart. (A) Showing the relationship of the pulmonary artery to the defect. (B) Showing the aorta away from the defect. D—Defect. Pu—Pulmonary artery. A—Aorta. P—One part of the parietal band.

divided into a septal portion, or the septal band, and a parietal portion, or the parietal band (crista supraventricularis of other authors[35]). Normally, the septal band ascends obliquely from the apicolateral region and terminates at the base of the pulmonic valve. There it is met by the parietal band which proceeds over the parietal (anterior) wall of the right ventricle in close proximity to the base of the anterior leaflet of the tricuspid valve. It ends in the trabecular formations of the right ventricle. Where the septal band meets the parietal band, there is sometimes seen a distinct raphé, previously described by Keith. There are numerous variations in the above pattern, such as the septal band being represented by two structures, and the parietal band being subdivided into various components, but their direction and relationships are normally constant.

This is not the case in overriding aorta complexes (tetralogy of Fallot and the Eisenmenger complex) (Fig. 7). In tetralogy of Fallot,[17] the most common pattern is that of the septal band being hypertrophied, and meeting a shortened and hypertrophied parietal band, which is deviated away from the tricuspid valve and on towards the anterior wall of the right ventricle, to produce a crista which limits the conus. A second parietal band joins the septal band beneath the ventricular septal defect and the base of the aorta to proceed over the parietal wall of the right ventricle in close proximity to the tricuspid valve. The other modifications of the architecture of the crista in tetralogy of Fallot and in partial transposition are out of the reach of the present considerations.

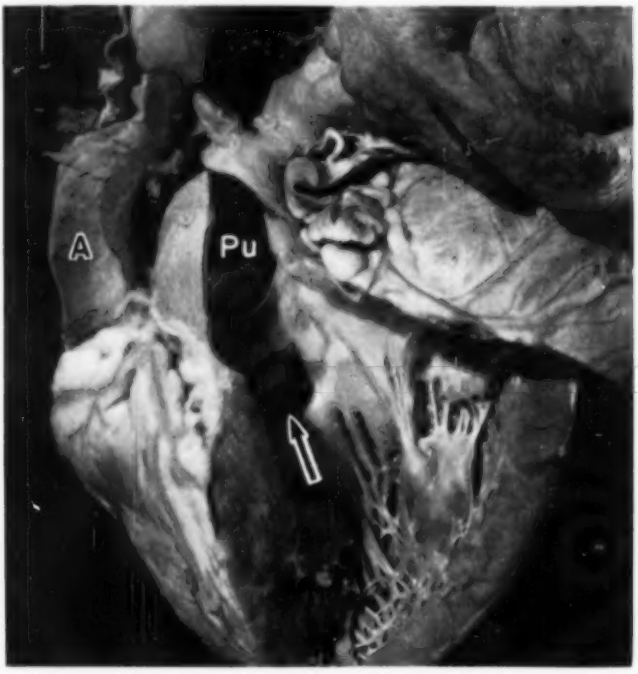

FIGURE 12: The defect in one type of complete transposition with normal architecture. Left ventricular view. A—Aorta. Pu—Pulmonary artery. Arrow points to the defect.

Hence the defect in tetralogy of Fallot enters the right ventricle in the region of the conus below (posterior to) the deviated, or at times the perforated, crista supraventricularis. The architecture of the right ventricle is therefore not the same as in isolated ventricular septal defect.

B. Eisenmenger complex (Fig. 9).[15, 17, 36-39] The term Eisenmenger complex is a pathologic one, and is not identical with the Eisenmenger syndrome of the clinicians. In the Eisenmenger complex, the relationships of the ventricular septal defect are again different from those of a true isolated ventricular septal defect. This defect again is in the anterior septum and the adjacent pars membranacea, and its upper margin is

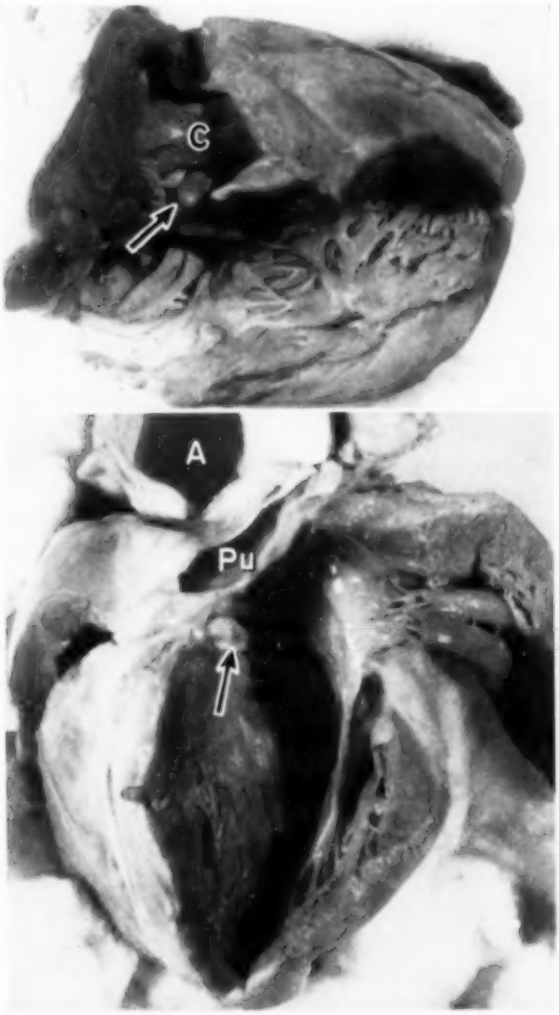

FIGURE 13A

FIGURE 13B

Figure 13: Pulmonary stenosis with ventricular septal defect and normal aortic root. (A) Right ventricular view looking up into the conus. (B) Left ventricular view. The defect here was guarded by a valve seen in both (A) and (B). C—Crista. Pu—Pulmonary artery. A—Aorta. Arrows point to the defect.

confluent with the opening of the base of the aorta. This defect likewise opens into the lower part of the conus of the right ventricle beneath the deviated crista. Hence the architecture of the right ventricle is different from that in the true ventricular septal defect, as is true of tetralogy of Fallot. However, there are many cases where the defect is associated with only mild overriding of the aorta and minimal architectural changes in the right ventricle. It is in these cases that from the anatomic side either the appellation Eisenmenger or isolated ventricular septal defect pertains. From the physiologic side, even a true Eisenmenger with marked overriding of the aorta, or even partial transposition of the Eisenmenger type,[17] may act physiologically like an isolated ventricular septal defect. Hence, from the standpoint of the clinician, the physiologic concept of the Eisenmenger syndrome is more pertinent than the pathologic concept of the Eisenmenger complex. The surgeon, however, may find it useful to be acquainted with the truly different anatomic type of Eisenmenger complex, and partial transposition of the Eisenmenger type (double outlet right ventricle with increased pulmonary flow).

C. Partial transposition (Fig. 10). In partial transposition, the defect is again large and is in the anterior septum and the adjacent part of the pars membranacea. Its upper margin is continuous with the left side of the rim of the aortic base. It opens proximal to and below the crista, which is deviated more over the anterior wall of the right ventricle. The architecture of the right ventricle is now markedly altered.

D. Truncus arteriosus communis persistens.[15-17, 40-44] Here the ventricular septal defect is of the same type as that seen in tetralogy of Fallot, and in the Eisenmenger complex, except that there is a greater involvement of the anterior septum, and less of the pars membranacea; the latter may even be intact.

E. Taussig-Bing heart (Fig. 11).[15-17, 45-47] Here the ventricular septal defect is large and situated high in the anterior ventricular septum, beneath the pulmonary artery. The architecture of the crista is such as to deviate the aorta away from the defect, while the pulmonary artery rides over the defect.

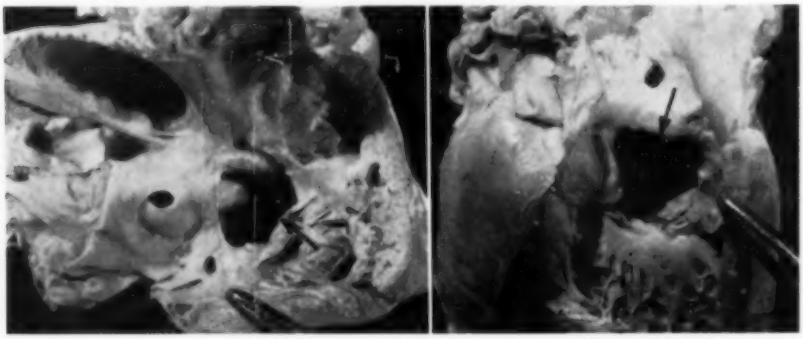

FIGURE 14A FIGURE 14B

Figure 14: The defect in common atrioventricular orifice. (A) Right sided view. (B) Left sided view. Arrows point to the combined defect.

F. Complete transposition with normal architecture (Fig. 12).[15-17, 48-51] Here the defect may be large or small, and is usually situated in the anterior part of the ventricular septum, and the anterior part of the pars membranacea. It is, however, often found in the posterior septum, proximally. Uncommonly, it is present elsewhere. The defect may have a close relationship to the pulmonary artery to produce a Taussig-Bing syndrome.

G. Complete transposition with single ventricle and small outlet chamber.[15-17, 52] The defect is present in the modified anterior ventricular septum, the posterior septum being absent. It may be large or small, but is usually the latter. Accordingly, the aorta which arises from the small chamber is usually smaller than the pulmonary artery.

H. Pulmonary stenosis with ventricular septal defect (normal aortic root) (Fig. 13).[15-17, 53-58] In the very few cases that the author has seen, the defect was present in the region of the pars membranacea, and the adjacent anterior and posterior ventricular septum. Its lumen was not confluent with that of the aorta. Thus the defect was of the type seen in isolated ventricular septal defect.

I. Common atrioventricular orifice (Fig. 14).[15-17, 23, 59-62] In this anomaly, as is well known, there is a single combined defect of the atrial and ventricular septum. The ventricular portion of this defect varies in size from minute to giant size, in the latter case altering the physiognomy of the left and right ventricles. The defect is situated in the posterior part of the ventricular septum, together with the pars membranacea. This defect is related to the root of the aorta only secondarily, in the region of the anterior component of the cleft anterior leaflet of the mitral valve.

J. Tricuspid atresia or stenosis without transposition (Fig. 15).[15-17, 63-65] The defect varies here from minute to large, and is usually situated in the region of the pars membranacea and the surrounding posterior ventricular septum. In some cases it involves the anterior septum.

In some of the above complexes, the ventricular septal defect may or does dominate the physiologic picture.[7, 52-56, 66] Thus, in tetralogy of Fallot

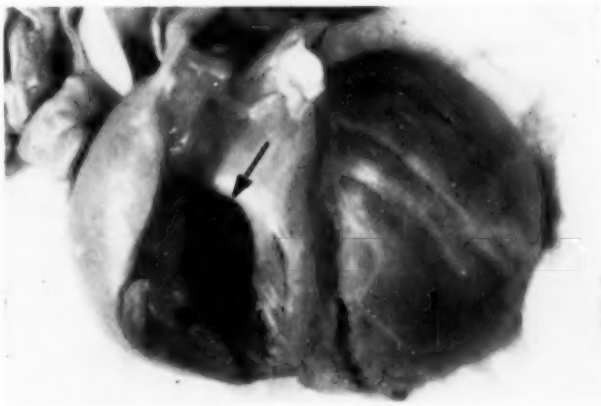

FIGURE 15: The defect in tricuspid atresia without transposition. Right ventricular view. Arrow points to the defect.

with left to right shunt, the left side of the heart may not be as small as in true cyanotic tetralogy. In the Eisenmenger complex, the ventricular septal defect does dominate the picture. In pulmonary stenosis with ventricular septal defect and normal aortic root, and left to right shunt, the defect dominates the scene. In common atrioventricular orifice, the relationship of the size of the ventricular septal component of the common septal defect to the overall pathology of hypertrophy remains to be analyzed. In the rare tricuspid stenosis with increased pulmonary flow, the size of the defect is the important anomaly.

SUMMARY

1. The anatomic locations of the various types of ventricular septal defects are described, as related to the embryologic components of the ventricular septum, and the relationship of the defect to the aorta, pulmonary artery, and the crista supraventricularis.

2. The importance of the architecture of the muscle bundles of the right ventricle is reemphasized.

3. The isolated small ventricular septal defect is important pathologically because of its complications.

4. The isolated large ventricular septal defect, as seen at autopsy, produces right ventricular hypertrophy, and frequently but not always, left ventricular hypertrophy.

5. There are true anatomic Eisenmenger type complexes whose morphology differs from that of isolated ventricular septal defects.

6. The ventricular septal defect in tetralogy of Fallot, pulmonary stenosis with ventricular septal defect, and rarely tricuspid stenosis without transposition may dominate the physiologic picture.

Acknowledgment: Figures 3, 5, 8-11, 13-15 are from Lev, M.: *Autopsy Diagnosis of Congenital Malformed Hearts* by courtesy of Charles C Thomas, publisher, Springfield, Illinois.

RESUMEN

1. Se hace una descripción de la localización de los varios tipos de defectos del tabique ventricular, en relación con los componentes embriológicos del septum ventricular y en relación con los defectos aórticos, de la arteria pulmonar y de la cresta supraventricular.

2. Se recalca la importancia de la arquitectura de los haces musculares del ventrículo derecho.

3. El defecto septal ventricular pequeño es patológicamente importante por sus complicaciones.

4. El defecto grande aislado, ventricular en el septul tal como se ve en la autopsia produce hipertrofia ventricular derecha y frecuentemente, pero no siempre, hipertrofia ventricular izquierda.

5. Hay verdaderos complejos anatómicos de Eisenmenger cuya morfología difiere de la de los defectos ventriculares aislados.

6. El defecto septal en la tetralogía de Fallot, estenosis pulmonar con defecto septal ventricular y rara vez estenosis tricuspídea sin transposición, puede dominar el cuadro fisiológico.

RESUME

1. L'auteur décrit les localisations anatomiques des différentes malformations de la paroi ventriculaire, selon les composantes embryologiques de cette paroi. Il montre également les relations possibles avec les anomalies de l'aorte, de l'artère pulmonaire, et de la crête supraventriculaire.

2. L'importance de l'architecture des faisceaux musculaires du ventricule droit est de nouveau signalée.

3. La petite malformation isolée de la paroi ventriculaire est importante en fonction de ses complications.

4. La malformation isolée de la paroi ventriculaire de volume important, comme on en voit à l'autopsie, entraine une hypertrophie ventriculaire droite, et fréquemment, mais pas toujours, une hypertrophie ventriculaire gauche.

5. Il existe de vrais complexes anatomiques type Eisenmenger dont l'aspect est différent de celui de ces anomalies isolées de la paroi ventriculaire.

6. La malformation de la paroi ventriculaire dans la tétralogie de Fallot, sténose pulmonaire avec altération de la paroi ventriculaire, et rarement une sténose tricuspidienne avec transposition peuvent dominer le tableau au point de vue physiologique.

ZUSAMMENFASSUNG

1. Beschreibung der anatomischen Lokalisierung der verschiedenen Arten von Kammerseptumdefekten in Beziehung zu den entwicklungsgeschichtlichen Komponenten der Kammerscheidewand, sowie der Beziehung der Defekte der Aorta, art.pulm. und der Crista supraventricularis.

2. Die Wichtigkeit des Aufbaues des Muskelbündels des rechten Ventrikels wird erneut betont.

3. Der isolierte kleine Kammerscheidewanddefekt ist pathologischanatomisch bedeutsam wegen seiner Komplikation.

4. Der isolierte grosse Kammerscheidewanddefekt, wie man ihn auf dem Sektionstisch sieht, führt zu einer Hypertrophie der rechten Kammer und häufig, aber nicht immer, auch zu einer solchen des linken Ventrikels.

5. Es gibt echte anatomische Komplexe vom Eisenmenger-Typ, deren Morphologie verschieden ist von der von isolierten Kammerscheidewanddefekten.

6. Die Kammerscheidewanddefekte der Fallot'schen Tetralogie, Pulmonalstenose mit Kammerscheidewanddefekt und selten auch Tricuspidal-Stenose ohne Transposition können das physiologische Bild beherrschen.

References will appear in author's reprints.

An Improved Method of Coronary Arteriography*

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Upon inspection of current mortality tables, even the most phlegmatic must agree that there is a clear and compelling reason for improving our therapeutic approach to coronary occlusive disease. Add to this the untold suffering and disability resulting from coronary occlusion and the argument literally becomes a "clarion call that brooks no denial."

Since coronary insufficiency is a result of vascular narrowing, *coronary surgery* appears to be the most promising avenue of attack. Although relatively few patients might have sufficiently localized lesions to justify surgery, even a small proportion of the half million fatal cases each year would represent a worthwhile salvage. However, if coronary surgery is to be rationally applied, there must first be a means for determining which patients are suitable candidates for operation. No method short of actual visualization—either by radiological technics or under direct inspection—can accomplish this important objective. Thus, the desirability of a safe, easily-applied, and diagnostically-reliable method of preoperatively demonstrating diseased coronary arteries seems clearly established.

Historical

Reports of incidental as well as intentional radiological demonstrations of the coronary vessels date back at least to 1933, with Rousthöi[1] and Reboul and Racine[2] in the vanguard. Since that time, there have been numerous reports describing coronary arteriography in experimental animals. It appears that man's coronary arteries were first demonstrated during life by Radner[3] in 1945. The earliest large series of coronary visualizations in man, however, is attributable to Jönsson[4] who used retrograde thoracic aortography via a catheter inserted into a peripheral artery. Most of the retrograde aortograms in this series were done for the study of congenital cardiovascular abnormalities; coronary visualization was merely incidental. Other workers[5-12] have used various aortographic technics—including retrograde arterial catheterization, direct needle puncture of the ascending aorta, and transthoracic left ventricular needling—specifically for the purpose of demonstrating the coronary circulation. With each of these methods, successful demonstration of coronary vessels required invariably large and sometimes overwhelming doses of concentrated iodine-containing contrast media in order to counteract dilution effects. Even then, there was no assurance that the contrast medium would flow into one or both coronary arteries in sufficient concentration to pro-

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duce an adequate radiographic shadow. The uncertainty and poor quality of coronary visualization by these technics hardly justified the hazard. Occasional fatalities encountered by some investigators[13, 14] strengthened this conclusion and stimulated the present search for a more reliable and possibly safer method of visualizing the coronary arteries.

As has been stated, the major obstacle to coronary arteriography by former "brute force" methods is the problem of dilution. Related to this is the fact that high-velocity aortic blood flow wastefully shunts most of the contrast agent away from the coronary ostia and out into the systemic arterial tree. To avoid these problems, the present technic utilizes a balloon inflated in the ascending aorta, creating a small compartment above the aortic valve (Fig. 1). Contrast agent injected into this compartment must necessarily flow into the coronaries, or through the aortic valve, since there is no other escape route. As a result, the dose and concentration of opaque medium can be reduced and the predictability of adequate coronary opacification is much enhanced. At the same time, systemic toxic effects of the contrast medium are effectively eliminated.

The Technic

A general anesthetic, although not a rigid requirement, is desirable and has been used on all animals and human subjects to date. Provision is made for continuous electrocardiographic recording during the actual visualization procedure; this is probably more important for the operator's peace of mind than for the welfare of the patient. Prior to exposing the right radial artery, a modified[15] Type I Dotter-Lukas double-lumen balloon catheter (Fig. 2) is prepared by rinsing in heparin solution; the injection lumen is then filled with heparinized saline and connected to a syringe

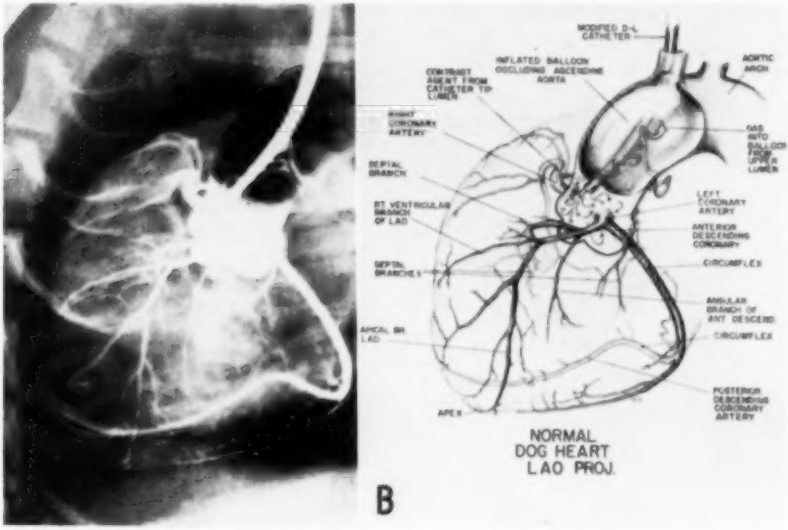

FIGURE 1A FIGURE 1B

Figure 1: Coronary arteriogram in the normal dog. A. Steep LAO view, immediately following injection of 5 cc. of 50 per cent Hypaque. Ascending aorta completely occluded by balloon containing 15 cc. of N.O. B. Diagrammatic representation of A, showing detail of occluding balloon as well as coronary arteries.

containing the same mixture. After the radial artery has been exposed, the catheter is introduced through a small transverse incision and passed proximally under fluoroscopic control until the tip lies in the ascending aorta, approximately one inch above the aortic valve. This part of the procedure is greatly facilitated by a Philips "Surgex" image-intensifying fluoroscope since the hazard and inconvenience of a dark room are eliminated. In any event, the importance of fluoroscopy can hardly be overemphasized since otherwise the tip of the catheter may not enter the

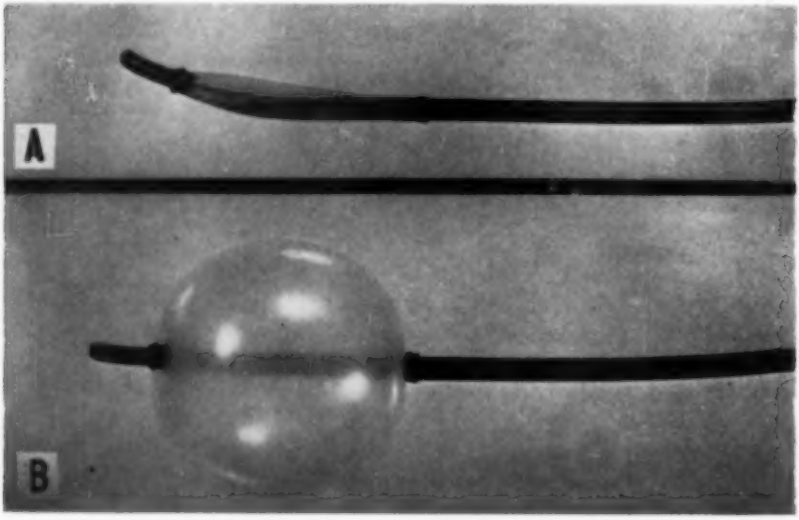

FIGURE 2: Type I Dotter-Lukas double-lumen balloon catheter. A. Distal end of catheter with undistended balloon. B. Same catheter after inflation of balloon with 15 cc. of N_2O.

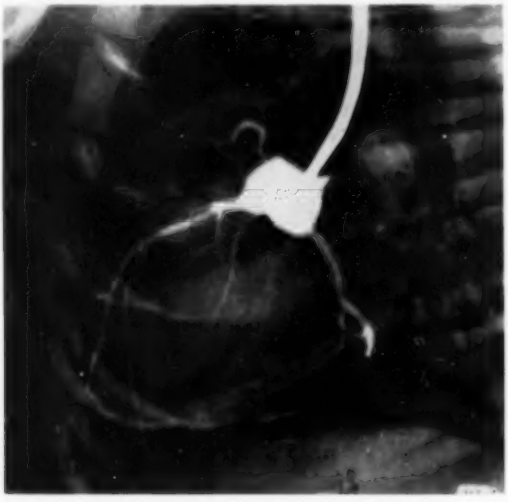

FIGURE 3: Single-exposure coronary arteriogram: Dog No. 16R. Serial films are preferred although a single exposure will suffice in most cases.

ascending aorta, it may pass into the left ventricle, or it may become lodged in one of the coronary orifices.

Once the catheter has been properly positioned, trial inflation of the balloon is accomplished using either nitrous oxide or carbon dioxide (approximately 15 cc. for the dog; up to 50 cc. for the larger balloon required for human use). Air should *not* be used for this purpose because of potential embolism if the balloon were to burst. The effectiveness of trial inflation is checked by palpation of the carotid arteries. Total aortic occlusion is the objective and is indicated by complete bilateral disappearance of the carotid pulse. If necessary, several trial inflations may be performed without hazard, but each attempt should be of short duration (5-10 seconds) with a short interval between separate occlusions.

After the quantity of gas required for total aortic occlusion has been ascertained, coronary arteriography may be commenced. The balloon is rapidly inflated, then the contrast medium is injected as fast as possible through the second lumen of the catheter. The contrast agent can easily be injected by hand for coronary arteriography in the dog since only 3 to 6 cc. are required. The larger doses necessary for visualization in the human subject (10-20 cc.) require the use of pressure-injection apparatus. Serial radiography is initiated at the beginning of injection and continued at a rate of one or two films per second for approximately six seconds. The

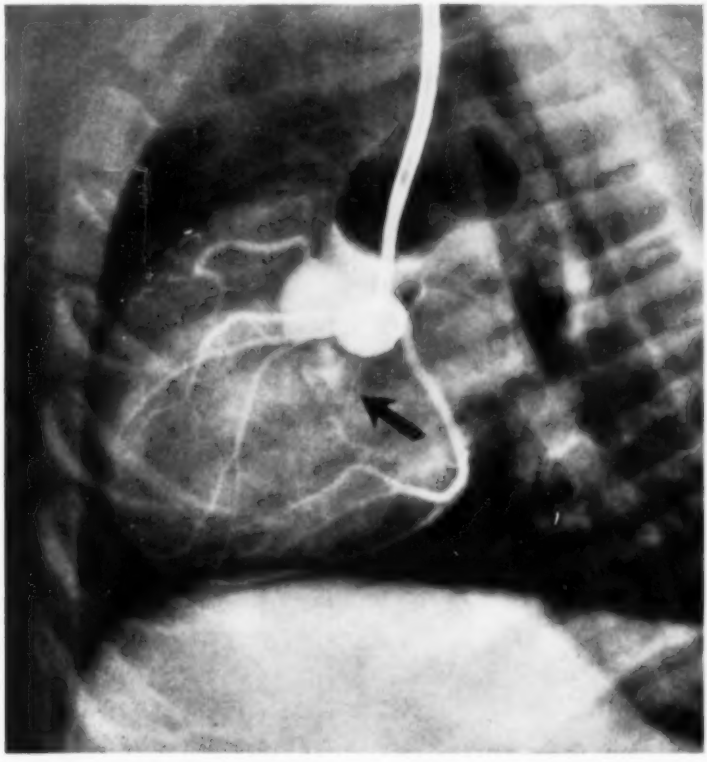

FIGURE 4: Coronary arteriography with 4 cc. Thorotrast. Slight aortic insufficiency (arrow) does not interfere with good visualization of coronary arteries.

occluding balloon is deflated following injection of contrast medium, even before the radiographic series is completed. Deflation of the balloon should be prompt but the piston of the syringe must not be forcibly retracted, else a portion of the balloon might be aspirated into the lumen of the catheter. Once the radiographic sequence is completed and the balloon has been deflated, the catheter may be removed and the artery repaired.

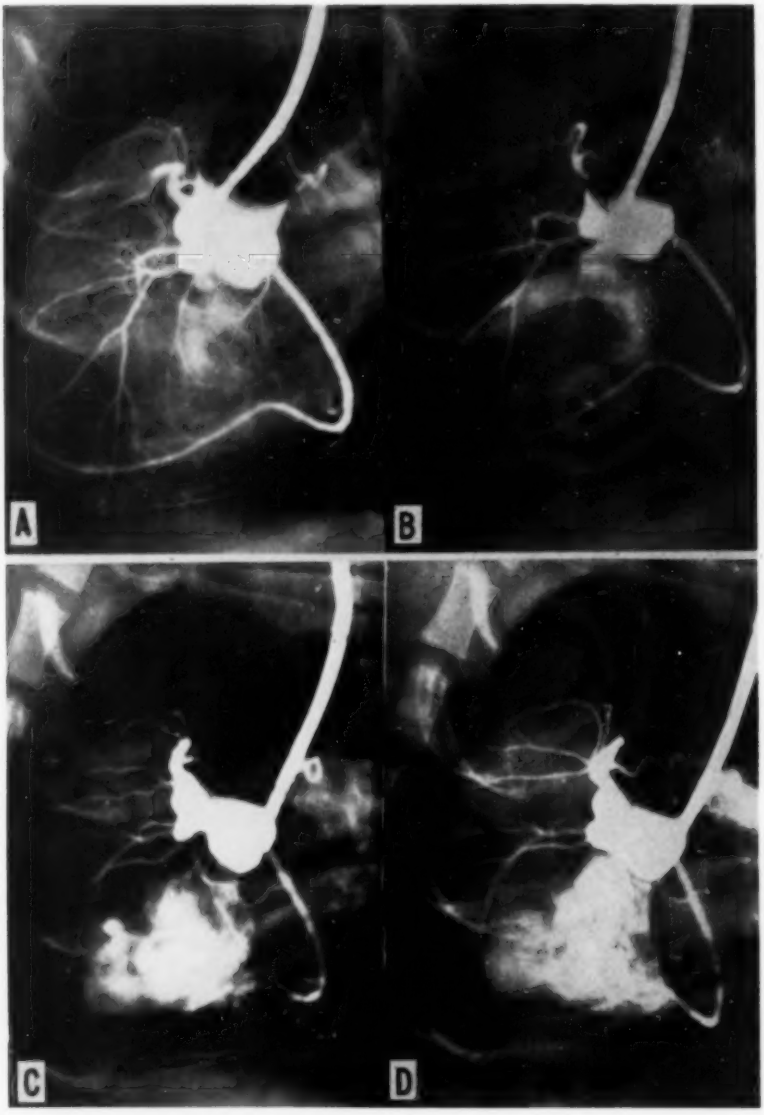

FIGURE 5: Serial coronary arteriograms by the technic of occlusion aortography. A and B. Films at ½ second intervals following injection of 8 cc. Thorotrast; moderate AI is shown. C and D. Technic same as above; marked AI partly obscures coronaries. Balloon is too large and not concentric with catheter.

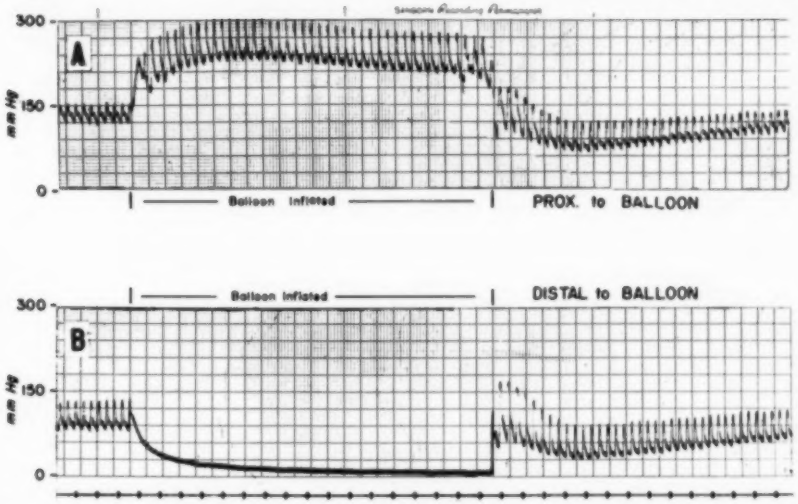

FIGURE 6: Blood pressure response to total ascending aortic occlusion in the dog. Tracings show effect of 15 seconds' occlusion in dog No. 9.

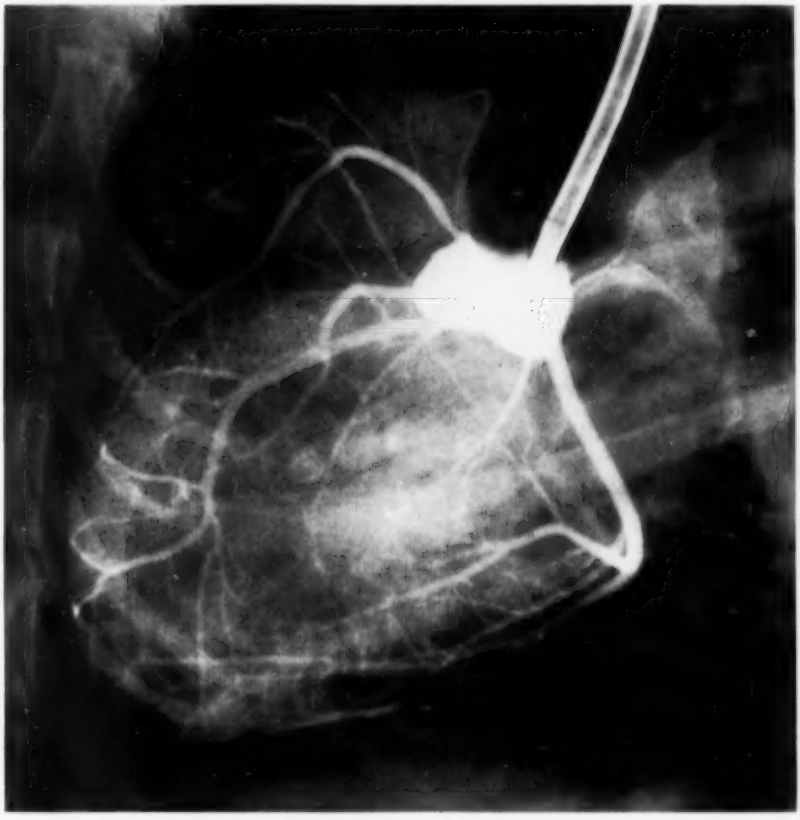

FIGURE 7: Acetylcholine-induced cardiac arrest used in conjunction with occlusion aortography. Excellent detail of finer coronary radicles, including intercoronary anastomoses. Slight "myocardial blush" equivalent to capillary phase of cerebroarteriography, is shown.

DISCUSSION

Considerable experience in the experimental laboratory has shown that this technic is capable of producing excellent coronary visualization in virtually every instance (Figures 1A, 3, 4, and 5). Since contrast medium is not permitted to escape into the systemic circulation, only small doses of dilute agents are necessary for highly detailed arteriograms. The hazard of myocardial damage is thereby materially reduced. Still further reduction of hazard may be achieved by substituting Thorotrast—a contrast medium of inadequate opacity when injected into the *unoccluded* aorta—for the more toxic iodine-containing media. In this connection, experimental evidence shows that Thorotrast has no more effect upon the myocardium than does normal saline. The weak radioactivity of Thorotrast is not believed to be objectionable in the required dose-range, particularly when the age and poor prognosis of most patients with coronary disease are considered. The possibility of a local tissue reaction resulting from extravasation of Thorotrast is not a problem with this technic since an intra-aortic catheter is used for the injection.

The effects of complete ascending aortic occlusion have been evaluated in 76 dogs, involving more than 1000 such occlusions. Electrocardiographic tracings (AVR, AVL and AVS, recorded simultaneously) were made in 236 instances. Blood pressure recordings were obtained both proximal and distal to the site of occlusion in the majority of experiments. No animal died as a result of aortic occlusion, nor were significant electrocardiographic changes observed in response to it. With the onset of occlusion, systolic blood pressure invariably rose proximal to the balloon and quickly stabilized at a level approximating twice the control value. Diastolic pressure also increased, but to a lesser extent, with a corresponding increase in pulse pressure (Figure 6A). Distal to the balloon, there was a prompt fall in blood pressure, reaching a plateau at approximately 30 mg. Hg. (Figure 6B). Recovery to normal levels of blood pressure was rapid and complete in all instances shortly following deflation of the balloon.

The effects of various contrast media—including Hypaque, Renografin, Urokon, Miokon, and Thorotrast—were assessed by means of blood pressure tracings and electrocardiograms. None of the contrast media appeared to have a consistent effect upon the blood pressure. Electrocardiographically, it was found that the iodine-containing media produced changes suggesting myocardial irritability or anoxia in direct proportion to the dose given. Thorotrast, on the other hand, usually produced no detectable electrocardiographic alteration. With the exception of several instances in which massive over-doses were deliberately given, no fatalities resulted with any of the contrast agents. The experimental studies were later extended to a series of 14 animals which had survived surgical ligation of the left anterior descending coronary artery or one of its major branches. Coronary arteriography, performed from one to thirty-four days following surgery, was equally well-tolerated in this group.

Application of occlusion aortography to human patients has been tried in only two individuals. In each case, attempts to produce total aortic occlusion were unsuccessful because the balloon was repeatedly swept into the descending aorta. Although the problem could be solved with a larger balloon and more rigid catheter, a more promising approach utilizing acetylcholine-induced cardiac arrest is presently under investigation. The possibilities in this approach were first suggested to us by Bailey and Lehman* who gave original credit to Arnulf. The applicability of acetylcholine-induced cardiac arrest to open-heart surgery has already been well-established by workers such as Moulder,[16] Mondini[17]; Lam,[18] and others.[19, 20] Our own results in a large series of laboratory animals (to be reported elsewhere) indicate that acetylcholine-induced cardiac arrest, used in conjunction with ascending aortic occlusion, not only improves coronary visualization (Figure 7) but is technically simpler and appreciably more predictable than occlusion aortography alone. Based on this experience, there is reason for believing that the addition of induced cardiac arrest to the technic herein described will further simplify coronary arteriography in the human subject and possibly decrease the risk as well.

SUMMARY

Vital statistics are an impressive argument for the development of a direct surgical attack upon coronary heart disease. A necessary prerequisite to such an attack is a safe method for clearly and predictably visualizing the coronary arteries prior to surgery.

Considerable experimental work has shown that occlusion aortography, with injection of contrast medium proximal to an occluding balloon within the ascending aorta, meets the above requirements. Used in conjunction with this technic, acetylcholine-induced cardiac arrest may be expected further to improve the results.

RESUMEN

Las estadísticas vitales constituyen un argumento impresionante para que se intente un ataque directo del problema por la cirugía en la enfermedad de las coronarias. Un requisito indispensable para abordar este problema quirúrgicamente, es el contar con un método seguro para ver las coronarias antes de la cirugía.

*Bailey, Charles P. and Lehman, J. Stauffer: Personal communication, June, 1957.

Se ha hecho mucho trabajo experimental para la aortografía por oclusión del medio de contraste proximalmente a una ampolla oclusora dentro de la aorta ascendente y esto llena el requisito antes mencionado. La detención cardiaca provocada por la acetilcolina en conjunción con esta técnica puede mejorar aún los resultados.

RESUME

Des statistiques de survie, on peut tirer un argument impressionnant pour le développement d'un traitement chirurgical direct de la maladie coronarienne. Un bilan indispensable pour un tel traitement est la méthode de sécurité: elle consiste à mettre en évidence les artères pulmonaries avant l'acte chirurgical.

Un travail expérimental considérable a montré que l'aortographie par occlusion, avec injection d'un milieu de contraste à proximité d'un ballon occlusif disposé dans l'aorte ascendante, réalise les conditions ci-dessus. On peut s'attendre à ce que l'arrêt cardiaque par l'acétylcholine, utilisé en association avec ce procédé, améliore les résultats.

ZUSAMMENFASSUNG

Lebensstatistiken sind ein eindrucksvolles Argument zu Gunsten der Entwicklung eines direkten chirurgischen Vorgehens bei Herzkranzgefäss-Erkrankungen. Eine notwendige Vorbedingung für ein solches Vorgehen ist eine sichere Methode für eine klare im voraus bestimmbare Darstellung der Coronararterien vor der Operation.

Beträchtliche experimentelle Arbeiten haben ergeben, dass eine Oklusions-Aortographie mit der Injektion des Kontrastmittels Proximal von einem verschliessenden Ballon innerhalb der aufsteigenden Aorta die angeführten Voraussetzungen erfüllt. Bei Verwendung in Verbindung mit dieser Methode kann man erwarten, dass eine durch Acetylcholin erzeugter Herzstillstand die Ergebnisse noch weiter verbessert.

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Single Catheter Gravity Drainage of the Right Atrium or Right Ventricle During Total Cardiac Bypass

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The currently employed cannulations preparatory to establishing cardiac bypass with the aid of a pump-oxygenator, include isolation of the superior and inferior vena cavae over tapes and the insertion of catheters into each of these vessels.[1-3] At the onset of bypass the caval tapes are tightened around the indwelling catheters and venous drainage is effected by suction applied to the venous line by one of a variety of pumps. During procedures in which the right atrium or right ventricle is opened the venous return to these cavities through the coronary sinus or Thebesian veins is commonly aspirated by low pressure suction and injected into the venous line by pump action.

Some workers[4, 5] have advocated gravity drainage of the venous return after insertion of individual caval catheters as described. They have described a smoother operation with absence of venous flutter as advantages of this method.

Paneth[5] has obtained direct measurements of total venous return through gravity siphon drainage of individual catheters placed in each cava, and in the right atrium and has found that these measurements reflected accurately the arterial pump output over a wide range of perfusion rates. Blood loss during perfusion was accurately reflected in a corresponding reduction in venous return and could be replaced quantitatively from an appropriate reservoir.

Our laboratory and clinical experience with the direct approach to the aortic and mitral valves suggested a simplification of this gravity drainage system. It consists of siphonage of total venous return through a single catheter inserted in the right atrium or in the right ventricle. Such drainage is applicable only to bypass employed during operative procedures on the left heart chambers or ascending aorta.

Experimental Methods

Series I: Adult mongrel dogs were anesthetized, intubated and attached to mechanical respirators. The right femoral artery was cannulated with a no. 14 or no. 15Fr plastic catheter. Right thoracotomies through the fifth intercostal space or midline sternum-splitting incisions were employed. Upon entering the chest the right auricular appendage was encircled with a purse string suture and total venous drainage obtained by inserting a no. 28Fr multiple-hole plastic catheter into the right atrium

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and draining this catheter by gravity siphonage into a reservoir placed between 40 and 50 cm below the operating table level. Extracorporeal circuits varied as follows:

1. In nine animals a double Sigmamotor pump and a bubble oxygenator were employed (Fig. 1).

2. In six animals the autogenous lungs were used in their normal oxygenating capacity necessitating cannulation of the pulmonary artery and left atrium (Fig. 2). Details of this procedure will be described elsewhere.[6]

At the onset of bypass the pulmonary artery was clamped at its base. Direct exposure of the aortic valve was obtained after inducing cardiac

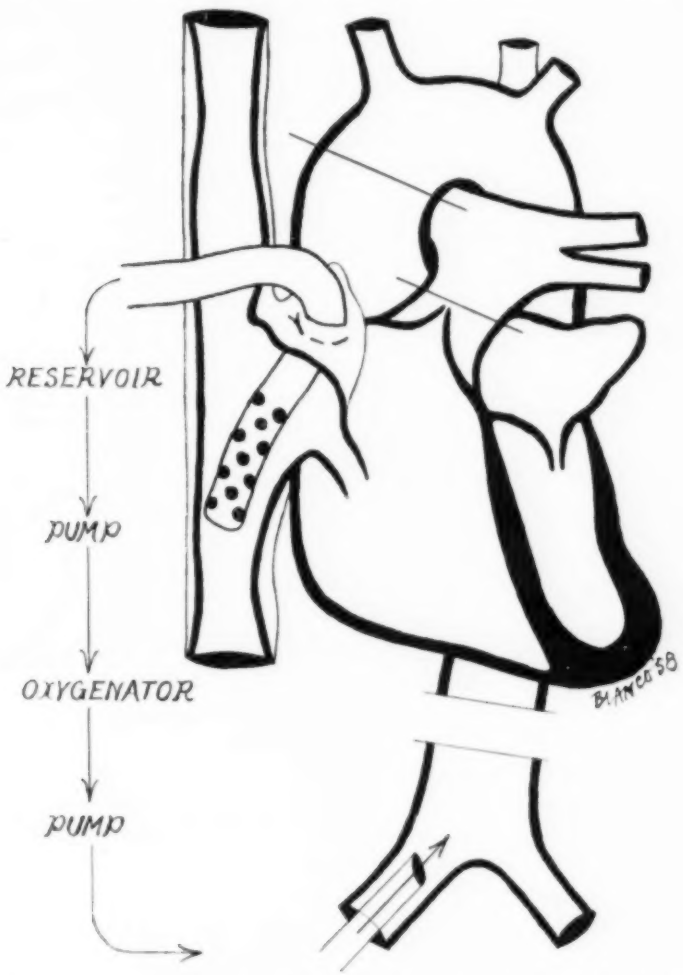

FIGURE 1: Venous blood is drained by a single catheter in the right atrium into a reservoir about 40 cm below table level. From here it is pumped through an oxygenator and then by a second pump head into the femoral artery. Clamps are placed at the base of the pulmonary artery and in the ascending aorta if the latter is to be entered.

arrest by the Melrose technique. Arterial pressures were monitored throughout the experiments. Caval pressures were measured with water manometers before and during bypass.

Series II: Fourteen dogs were prepared in similar fashion except that left thoracotomies were performed through the fifth intercostal space. The left femoral artery was cannulated preparatory to perfusion. "Venous" drainage was obtained by inserting a no. 24Fr catheter through the right ventricular outflow tract and directing it proximally into the right ventricular cavity (Fig. 3). This catheter was secured with a purse string suture in the wall of the right ventricle and drained as previously described into a dependent reservoir. At the onset of bypass the pulmonary artery was clamped at its base to insure complete emptying of venous return. A pump-oxygenator circuit was employed and direct exposure of the mitral valve was obtained through an incision at the base of the left atrium. In five experiments cardiac arrest was induced by injection of potassium-citrate-blood mixture into the beating left ventricle after cross-clamping of the aorta. Arterial and venous pressures were obtained.

FIGURE 2

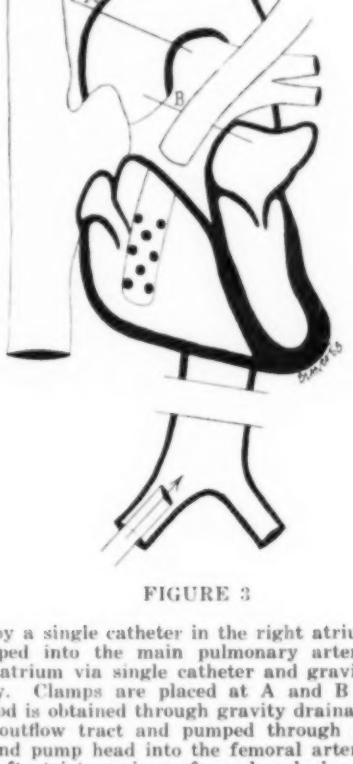

FIGURE 3

Figure 2: Venous blood is drained by gravity by a single catheter in the right atrium into a low reservoir. From here it is pumped into the main pulmonary artery. "Arterialized" blood is collected from the left atrium via single catheter and gravity drainage and pumped into the femoral artery. Clamps are placed at A and B if aortotomy is performed.—*Figure 3:* Venous blood is obtained through gravity drainage of a single catheter in the right ventricular outflow tract and pumped through an oxygenator from which it is pumped by a second pump head into the femoral artery. Clamps are placed at A before aortotomy or left atriotomy is performed and also at B if elective arrest is to be used.

Results

Gravity drainage of the right atrium or ventricle proved eminently satisfactory in all instances. Venous return under the circumstances described paralleled closely arterial pumping rates and reflected accurately the status of the total circulating volume. Blood losses were rapidly reflected in the blood level in the venous reservoir. By the same token, over-transfusion would cause an increase in reservoir blood. Venous pressures were typically 5 to 10 cm lower than those recorded before bypass. Arterial pressures were kept at mean values between 60 and 110 mm Hg during perfusion by employment of flow rates between 50 and 70 cc/Kg/min.

Clinical Cases

Since October 8, 1957, 16 patients have been operated upon using cardiopulmonary bypass with a pump-oxygenator and single catheter gravity

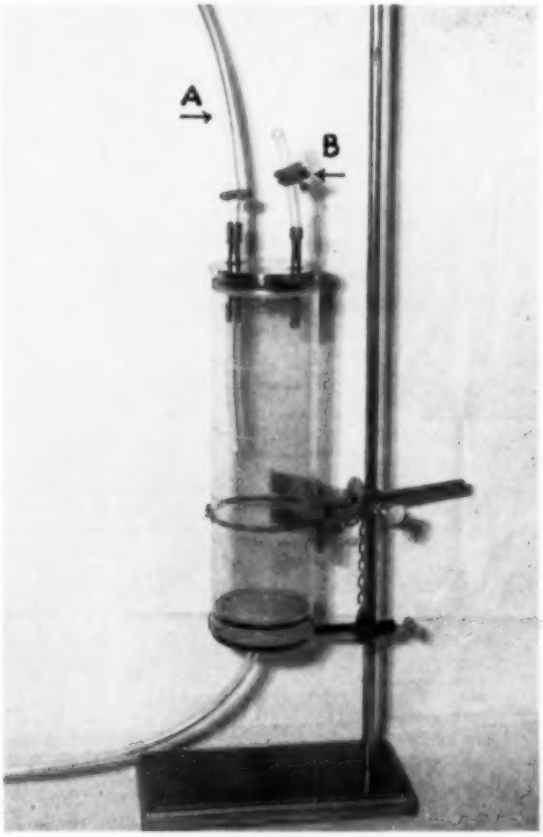

FIGURE 4: The gravity reservoir employed, showing the drainage line A and the special metal top which allows the elective establishment of suction by closing the clamp at B. This is particularly useful in cases where siphonage is broken by malposition or dislodgement of the drainage catheter.

drainage. In 13, direct correction of aortic stenosis or insufficiency was carried out. One patient underwent open, transaortic coronary endarterectomy. These procedures were carried out employing elective potassium arrest and, in all, the "venous" catheter was inserted into the right atrium.

Two patients were operated upon for correction of severe mitral regurgitation. Polar cross fusion of the mitral annulus was performed as described by Nichols.[7] Because of the advanced status of the valvular lesion, and the presence of large, tense, left atria which would make the usual techniques difficult, it was felt that cardiopulmonary bypass would provide a wider margin of safety and facilitate the operative maneuvers. Accordingly, a large catheter (no. 38 or no. 40Fr) was inserted into the outflow tract of the right ventricle and secured with a purse string suture. "Venous" blood was thereby drained by gravity into a reservoir from where it was pumped through an oxygenator and into the right femoral artery. A left posterolateral thoracotomy through the fifth interspace was used. The closed manipulations and placement of sutures across the incompetent mitral valves were tremendously facilitated by the bypass. Cardiac contractions persisted throughout, and were restored to normal strength as soon as bypass was terminated.

Again, our clinical experience with this method of "venous" drainage was most gratifying. The only difficulty encountered arose during the open coronary endarterectomy. The atrial purse string became loose with consequent dislodgement of the catheter and exposure of the holes at its tip. Air was thus sucked into the drainage tubing breaking the siphon. With loss of siphonage the venous blood entering the right atrium proceeded through the right ventricle and pulmonary circulation to enter the left side of the heart and escape through the aortic incision. Profuse hemorrhage resulted and the operation had to be terminated by rapid closure of the aortotomy accompanied by massive blood replacement. Fortunately, the patient survived but this experience has driven home the importance of accurate placement and secure anchoring of the draining catheter.

Discussion

The results described have convinced us of the simplicity and effectiveness of these techniques in cardiac bypass for operations on the left heart. They lend themselves well to emergency situations arising during preliminary manipulations in contemplated open-heart procedures. Rapid cannulation of the right atrium or ventricle with a single catheter is much more expeditious than individual isolation of the cavae with positioning of catheters in each vein. In mitral valve surgery single catheter drainage of the right ventricle will allow the surgeon to use a left thoracotomy in place of the more traumatic bilateral incision.

Care must be exercised in the selection of the caliber of the drainage catheter and tubing inasmuch as this factor determines the capacity of the siphon system and therefore the maximum flow possible. We have found that a no. 40Fr plastic catheter connected to 7/16" I.D. Tygon tubing has a siphon capacity of well over 4,000 cc. per minute and is satisfactory for the highest flows we have employed to date. It is easy to establish the capacity of smaller catheters and tubing which might be used with lower flow rates.

SUMMARY

Conventional methods of cannulation preparatory to cardiac bypass with a pump-oxygenator involve individual catheterization of the vena cavae. Drainage is then instituted by pump action or gravity.

A method is presented whereby operations on left heart structures, such as the mitral valve or the aortic valve area, may be simplified through the use of single catheter drainage of the right atrium or right ventricle. Gravity siphonage is employed

and the "venous" blood is collected in a dependent reservoir from where it may be pumped into an artificial or a biological oxygenator. Laboratory experiences with this setup showed it to be a satisfactory device in circuits employing an artificial oxygenator and in others in which the animal's own lungs were the oxygenating element. Encouraged by these results, we have used the single catheter method of drainage in patients suffering from mitral or aortic valve lesions. Three precautions should be observed during its use:

1. This method is applicable only to surgery on left heart structures in the presence of an intact septum.

2. The catheter employed and the drainage tubing should have a siphoning capacity compatible with the perfusion flows contemplated.

3. Care should be exercised in the correct placing and anchoring of the drainage catheter to prevent interruption of siphonage during operation. A simple safety device designed to re-establish siphonage by suction is illustrated.

Addendum: Since submitting the original article, twenty-five "open" aortic procedures employing the autogenous lung and forty-one plications of the mitral annulus by the Nichols' technique, with by-pass support, have been performed. Also, in more than 50 operations on the aortic valve, the artificial pump oxygenator was employed. In all, single catheter drainage was used and proved to be singularly efficient and trouble free.

RESUMEN

Los métodos habituales de canalización previa a la derivación del paso del corazón con un oxygenador de bomba incluye la cateterización individual de las cavas. La canalización es entonces instituída la acción de la bomba o por gravedad.

Se presenta aquí un método por el cual en operaciones de corazón izquierdo tales como las de mitral o de válvulas aórticas, se puede simplificar la técnica por el uso de un sólo cateter que canaliza el atrio o el ventrículo derecho.

El sifón de gravedad se emplea y la sangre "venosa" se reúne en una depósito abajo de donde puede ser bombeado hacia un oxigenador artificial o biológico.

Las experiencias de laboratorio con este arreglo se mostraron satisfactorias en los circuitos que emplean un oxigenador y en otros en que los propios pulmones del animal actúan como oxigenadores. Alentados por estos resultados hemos usado este método en enfermos de lesiones mitrales o aórticas. Se deben observar tres precauciones:

1. Este método es aplicable sólo a la cirugía del lado izquierdo y en presencia de un septum intacto.

2. El cateter empleado y el tubo de drenaje deben tener una capacidad de sifón compatible con la corriente de perfusión que se espere usar.

3 Debe tenerse cuidado en la correcta colocación y el anclaje del cateter de drenaje para evitar la interrupción del mecanismo de sifón durante la operación. Un artificio sencillo usado para restablecer el sinfonado por succión se presenta ilustrado.

RESUME

Les méthodes habituelles de mise en place de canules préparatoires à la traversée cardiaque avec oxygénateur à pompe comprennent le cathétérisme de la veine cave. Un drainage est alors institué par l'action de la pompe ou de la pesenteur.

Les auteurs présentent une méthode par laquelle les opérations sur les éléments du coeur gauche, telles que valvule mitrale ou zone des valvules aortiques, peuvent être simplifiées grâce à l'emploi d'un drainage par simple cathétérisme de l'oreillette droite ou du ventricule droit. Le siphonage par pesanteur est utilisé et le sang "veineux" est recueilli dans un réservoir attenant d'où il peut être pompé dans un oxygénateur artificiel ou biologique. Les expériences de laboratoire faites avec ce procédé ont montré qu'il s'agit d'un moyen satisfaisant pour les circuits utilisant un oxygénateur artificiel et pour ceux qui utilisent des poumons d'animaux comme élément oxygénateur. Encouragés par ces résultats, les auteurs ont utilisé la méthode de drainage par simple cathétérisme chez les malades souffrant de lésions des valvules mitrales ou aortiques. Trois précautions doivent être observées pendant son emploi:

1. Cette méthode n'est applicable que pour la chirurgie des éléments du coeur gauche avec paroi intacte.

2. Le cathéter utilisé et le tube de drainage doivent avoir une capacité de siphonage compatible avec les perfusions envisagées.

3. On doit faire attention à la mise en place et à l'amarrage correct du cathéter de drainage pour éviter l'interruption du siphonage pendant l'opération. Un simple appareil de sécurité destiné à rétablir le siphonage par succion est proposé.
tiné à rétablir le siphonage par succion est proposé.

ZUSAMMENFASSUNG

Die konventionellen Methoden der Kanüleneinführung zur Vorbereitung eines kardialen Kollateralkreislaufes mit einem Pumpen-Oxygenator machen im einzelnen eine Katheterisierung der Vena cavae erforderlich. Die Drainage wird dann ins Werk gesetzt durch Pumpentätigkeit oder durch Schwerkraft.

Es wird über eine Methode berichtet, mit deren Hilfe Operationen an den Organen des linken Herzens, wie z.B. der Mitralklappe oder dem Gebiet der Aortenklappen, vereinfacht werden können durch die Verwendung einer einzigen Katheterdrainage des rechten Vorhofes oder des rechten Ventrikels. Es wird dann die Absaugung durch Schwerkraft benutzt, und das "venöse" Blut wird gesammelt in einem herabhängenden Reservoir, von wo es in einen künstlichen oder biologischen Oxygenator gepumpt werden kann. Laboratoriumuntersuchungen mit dieser Anordnung ergaben, dass sie eine befriedigende Einrichtung ist für künstliche Kreislaufsysteme sowohl bei Gebrauch eines Oxygenators als auch bei solchen, bei denen die eigene Lunge des Tieres das sauerstoffversorgende Element darstellt. Durch solche Resultate ermutigt, haben wir die Ein-Katheter-Methode der Drainage angewandt bei Kranken mit Läsionen der Mitral- oder Aortenklappen. Drei Vorsichtsmassregeln müssen jedoch bei ihrer Anwendung beobachtet werden:

1. Diese Methode lässt sich nur verwenden bei Operationen an Organen des linken Herzens, wenn das Septum intakt ist.

2. Der Katheter und das Drainageröhrensystem müssen ein Saugvermögen haben, das der beabsichtigen Durchströmungsgeschwindigkeit angemessen ist.

3. Es muss Sorge getragen werden für eine korrekte Placierung und Befestigung des Drainagekatheters, um eine Unterbrechung der Absaugung während der Operation zu vermeiden. Es wird eine einfache Sicherheitsvorrichtung erläutert, die dazu bestimmt ist, die Aushebung durch Ansaugung wieder in Gang zu setzen.

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CURRENT THERAPY

The Rationale of Vasopressor Treatment of Cerebrovascular Insufficiency and Coronary Insufficiency

The results of several studies have left no doubt that vasopressor drugs are effective in reducing the incidence and severity of cerebral and myocardial necrosis and the mortality in patients with acute cerebral vascular and coronary insufficiency.[1-8] Until recently, the use of vasopressor drugs for these conditions has been largely empirical or theoretical. However, the mechanism of their action has now been worked out.[9] It has been shown that they cause a redistribution of the circulating blood flow to the vital organs in a most economical fashion at a time when the total circulating blood volume is diminished.

In 1949,[1] it was demonstrated in the beating heart that the coronary circulation was markedly diminished in shock and, when coronary occlusion or narrowing was present, the myocardium normally supplied by the diseased artery failed to contract and actually ballooned outwards in systole because of a failure of the collateral circulation. When the blood pressure was restored, the myocardium, which had been ballooning, again contracted in an effective fashion. It was demonstrated by fluorescein dye and radioactive isotope techniques that the collateral circulation may be sufficient to nourish the ischemic myocardium following a coronary artery ligation; however, when hypotension also occurred, this collateral circulation failed. In other studies,[7a, 7b] it was demonstrated that the collateral circulation of the brain also fails during hypotension; but when vasopressor drugs restored the systemic blood pressure, the collateral circulation was reestablished and the signs and symptoms of cerebral ischemia disappeared.

To determine the effect of hemorrhagic and traumatic shock and vasopressor drugs on the regional circulation of the vital organs, the blood flows of the carotid artery, coronary artery, hepatic artery, portal and renal veins were measured simultaneously in a dog.[9] During the hypotensive state of shock, the blood flow of each of these vital organs was markedly depressed. However, immediately following the induction of acute hypotension, the blood pressure increased spontaneously as much as 20 to 50 mms. of Hg. It was determined that, during this period of "compensation," the coronary artery, hepatic artery, and usually carotid artery flows increased in a linear fashion; but at the same time, the renal and portal vein flows diminished. In other words, the blood pressure was partially restored during this period of compensation by an increase in the vascular resistance of the mesenteric and renal circulations. Following stabilization of the blood pressure, vasopressor drugs were then administered intravenously. It was now noted that the vasopressor drugs further increased the carotid, coronary and hepatic artery flows but that the renal and portal circulations dropped even further. It is thus apparent that the vasopressor drugs restore the systemic blood pressure by increasing the vascular resistance in the renal and mesenteric circulations. This results

in an increased flow to the cerebral and coronary circulations and in the hepatic artery flow. This is probably the most economical redistribution possible during the hypotensive period of shock. The circulating blood volume, which is diminished, is now directed mainly to the brain and heart, which are the organs least able to withstand ischemia for long periods of time and which are the most vital for survival. A vasopressor drug such as levarterenol can increase coronary flow as much as 500 per cent by reducing the resistance of the peripheral coronary bed[8] in addition to raising the blood pressure.

The diversion of blood away from the renal and mesenteric circulations which occurs during severe hypotension is exaggerated by vasopressor drugs. Thus, the use of these agents may increase the tendency to renal and intestinal necrosis which is sometimes observed in shock. The danger of hepatic necrosis due to vasopressor drugs, however, is slight. Although the portal venous flow is reduced, the hepatic artery flow, which supplies 70 per cent of the liver's oxygen supply, is enhanced by vasopressor therapy.

Treatment of Myocardial Ischemia with Vasopressor Drugs

It has been reported that sustained, severe shock due to acute myocardial infarction in the human is attended by a mortality rate of 80 to 90 per cent.[1-6] When vasopressor drugs are used to combat the hypotension, the mortality rate is reduced to 47.8 per cent.[1-6] Vasopressor drugs increase the coronary flow not only because they restore the blood pressure but, in addition, drugs like levarterenol cause a marked increase in coronary flow above that which may be anticipated with a blood pressure change because they reduce the resistance of the peripheral coronary bed. This vasodilating action of levarterenol which may increase the coronary flow 500 per cent would reduce the ischemia of the myocardium.[8] Clinicians have been advised to start these vasopressor drugs as soon as the blood pressure drops to a systolic level of 80 mms. of Hg. Our experience indicates that it is difficult to tell at what level the vasopressor agent should be started. We have demonstrated that a drop in blood pressure from 100 to 80 mms. of Hg. will often diminish the coronary flow one-third.[8, 11] In many patients, such a reduction in coronary flow will result in congestive heart failure or cardiac arrhythmias. Cardiac decompensation and arrhythmias may be corrected immediately upon restoration of the blood pressure. For this reason, the clinician should start the vasopressor drugs at a level even above 80 mms. of Hg. if cardiac decompensation or irregularities appear. The mortality rate and degree of myocardial damage due to ischemia will probably be reduced even farther if vasopressor drugs are started at higher blood pressure levels when congestive failure or cardiac irritability supervenes.

We have observed certain electrocardiographic alterations in the normal intact dog's heart when vasopressor drugs were administered in traumatic shock. These changes consisted of the appearance of ST segment elevations and coved T wave inversions similar to those noted in acute myocardial infarction.[8] These electrocardiographic changes promptly disappeared when the vasopressor drugs were discontinued. They probably resulted from a potassium or electrolyte shift in the myocardium due to an alteration in membrane permeability associated with the pressor drug administration.

Treatment of Cardiac Arrhythmias with Vasopressor Drugs

Systemic hypotension may result from rapid supraventricular and ventricular tachycardias. We have demonstrated that when the blood pressure is restored during these arrhythmias, the coronary flow may return to normal even if the arrhythmia continues.[10, 11] Frequently, however, the tachycardia will terminate as soon as the systemic blood pressure is restored. It has been suggested that the restoration of blood pressure aborts the cardiac arrhythmias because of the increase in coronary irrigation or because of a stretching effect on the myocardium.[10, 11] We have successfully terminated supraventricular and ventricular tachycardias, sinus bradycardia, complete heart block, frequent premature systoles in patients following myocardial infarctions by simply restoring the systemic blood pressure with vasopressor drugs.[12] In instances where the arrhythmia could not be aborted in this manner, the restoration of blood pressures with the vasopressor drugs nevertheless enhanced the coronary blood flow. Thus, enough time was gained to allow correction of the arrhythmias with other antiarrhythmic agents. In one patient with severe hypotension and a supraventricular tachycardia following myocardial infarction, the systemic blood pressure was maintained for four days until antiarrhythmic agents eventually corrected the arrhythmia.[12] Vasopressor therapy of cardiac arrhythmias undoubtedly will result in a reduction in the high mortality rate of the arrhythmias when they are associated with myocardial infarction.

Treatment of Cerebral Ischemia with Vasopressor Drugs

Sudden cerebral ischemia is produced in patients with chronic cerebral thrombosis by hypotension, reduction in cardiac output, or hypoxemia. If hypotension occurs in the patient with cerebral artery narrowing or thrombosis, the collateral cerebral circulation fails and cerebral vascular insufficiency results. It has been demonstrated that about 12 per cent of cerebral infarctions are due to the hypotension associated with myocardial infarction which is often unsuspected. Other precipitating causes of cerebral vascular insufficiency are traumatic shock, hemorrhagic shock, anti-hypertensive drugs, hypersensitive carotid sinus, postural hypotension, reflex hypotension, cardiac arrhythmias, anaesthetics, congestive heart failure, pulmonary infarction, valsalva maneuver, angiography, and gravitational states.[7a, 7b] Many of these precipitating causes may be corrected simply by placing the patient in a prone position. However, it has been dramatically demonstrated that following a myocardial infarction with hypotension, neurological signs and symptoms will disappear immediately upon restoring the blood pressure.[7a, 7b] It has been shown experimentally that the electroencephalographic signs of ischemia will disappear immediately if the blood pressure is restored with levarterenol.[7a, 7b] The judicious use of vasopressor drugs in cerebral thrombosis and cerebral vascular insufficiency will probably reduce the neurological disturbances which so often cripple the patient.

Selection of Vasopressor Drugs

Vasopressor drugs may be administered orally, intravenously, or intramuscularly. Intravenous use of such drugs as levarterenol may result in a tissue slough due to vasospasm of the arterial circulation. Other agents

such as metaraminol which may be administered intramuscularly or intravenously are preferred by some because they do not cause this necrosis. Our experience indicates that levarterenol is probably the most effective vasopressor drug as it will often restore the blood pressure when other agents have failed. We have noted, however, with all vasopressor agents that if the blood pressure rises to hypertensive levels (above 180 systolic), it may result in serious cardiac arrhythmias such as ventricular fibrillation. This arrhythmic effect could also be caused experimentally by simply raising the blood pressure by placing a snare around the aorta.[10-12] We and others have observed these serious cardiac arrhythmias in patients receiving vasopressor drugs. For this reason, the use of a short-acting vasopressor agent such as levarterenol is advisable. Its pressor effect may be reduced immediately by slowing the rate of administration of the intravenous drip. We have seen instances of marked hypertension lasting up to one-half to two hours after the use of metaraminol intramuscularly and, during this period, have also witnessed serious ventricular arrhythmias resulting in death. Our experience indicates that it is safer to use a short-acting, more easily controlled vasopressor drug such as levarterenol in spite of the danger of a tissue slough.

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Hyperpotassemia

J. M., a 20 year old divorced white woman, was seen with the history of "swelling" of the feet and the face associated with dyspnea, orthopnea, and palpitation of six months duration. For three weeks, she was given 3 gms. of potassium chloride daily as a diuretic agent. For two days, she complained of "hoarseness," vomiting, difficulty in breathing, and marked weakness.

Physical examination revealed a pale orthopneic woman with a temperature of 99.8° F., and blood pressure 166/92. There was moderate cardiac enlargement and hepatomegaly. Laboratory evaluation demonstrated renal insufficiency, albuminuria and pyuria. There was a leukocytosis, marked anemia, azotemia, and acidosis. The admission electrocardiogram demonstrated a sinus tachycardia at a rate of 120 per minute. PR interval was 0.15 seconds. QS interval was 0.09 seconds. T1 was low and T2 and T3 were diphasic.

She had chronic pyelonephritis with uremia and potassium intoxication.

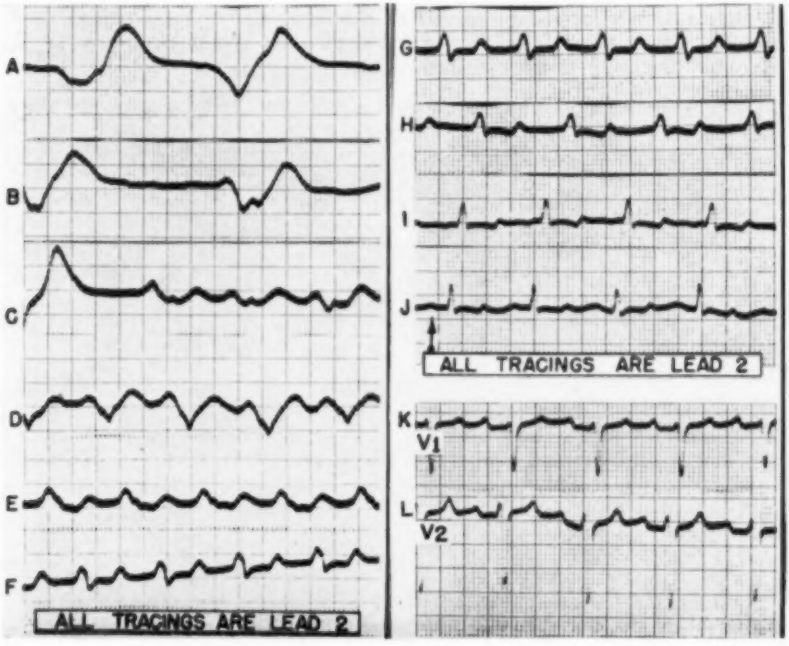
On the following day, she developed a peripheral pulse of 30 per minute associated with extreme "weakness" and inability to move her arms and legs. There was marked dyspnea, "blurring" of vision, and a "choking" sensation. Respirations were 36 per minute and shallow. An electrocardiogram showed sinus arrest with an idioventricular rhythm at a rate of 32 per minute.

The following electrocardiographic changes were observed with therapy (figures 1 and 2):

(A) Complete sinus arrest with an idioventricular rhythm at a rate of 43 per minute. The merging of the T wave into the QRS complex demonstrates the large biphasic complex or sine wave suggestive of hyperkalemia.

(B) Immediately after 10 cc. of calcium gluconate was injected intravenously over a period of three and one-half minutes. The patient developed a severe headache with stertorous and labored respirations. There was a slight increase in the ventricular rate with periods of ventricular bigeminy.

(C) Twenty seconds after beginning an intravenous administration of 50 cc. of



isotonic saline solution, there was an abrupt change in the rhythm and the patient became alert, opened her eyes, the vision cleared, and she was able to move her extremities. The respirations relaxed, became full, and the oxygen was removed. The idioventricular rhythm increased to approximately 86 per minute with still no evidence of atrial activity.

(D) Immediately after the 50 cc. of saline infusion was completed. The QRS complexes are greatly prolonged with fusion of the T waves into the characteristic sine wave.

(E) One minute after the administration of 50 cc. of sodium chloride solution. The T waves are now beginning to demonstrate their independence of the QRS complex.

(F) One and one-half minutes after (D). There is no evidence of atrial activity, however, the QRS complex although prolonged to 0.19 seconds is now independent of the T waves.

(G) Eighteen minutes after (D). The QRS complexes are now 0.16 seconds and sharply defined.

(H) Twenty-seven minutes after the completion of the saline infusion. The T waves have become diphasic, yet there is no visible evidence of atrial activity.

(I) Forty minutes after (D) and ten minutes after the intravenous administration of 50 cc. of 50 per cent glucose. Atrial or nodal activity is beginning to express itself by a small biphasic P wave. The QRS complexes have increased voltage and their duration has shortened to 0.09 seconds.

(J) Seventy-four minutes after (D). There is a low prolonged P wave with a PR interval of 0.24 seconds characteristic of incomplete A-V block.

(K) and (L) Twenty-five hours after the administration of sodium chloride. The normal process of depolarization and repolarization of the myocardium is reestablished with the exception of a prolonged PR interval of 0.22 seconds.

Comment

The clinical and electrocardiographic findings are those of far advanced hyperpotassemia following the administration of potassium chloride to a patient with impaired renal output. The administration of calcium chloride had no definite antagonistic effect upon the inhibitory action of potassium on either cardiac or skeletal muscle, although there was evidence of increased ventricular irritability (B). On the other hand, the inhibitory effect of hyperkalemia on skeletal and cardiac muscle was dramatically and impressively neutralized by the addition of sodium chloride (C). Fifty cc. of 50 per cent glucose solution was administered in an effort to mobilize potassium in the liver (1).

This therapeutic lesson may be better remembered by the phrase "take your potassium with a grain of salt."

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X-RAY FILM OF THE MONTH

Clinical Information

The patient was a three month old colored boy with intermittent nonproductive cough and wheezing since the age of two weeks. There was no dyspnea or cyanosis. Physical examination was entirely negative, as were laboratory studies.

FIGURE 1: Inspiration and expiration films of the chest.

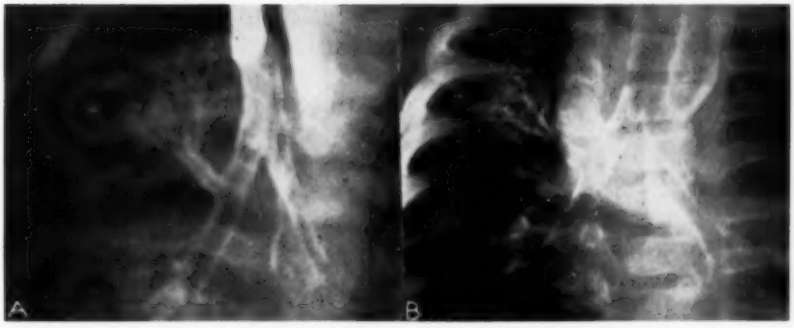

FIGURE 2: Anteroposterior and left anterior oblique views on bronchogram.

See page 568 for answer.

ANSWER

Agenesis of the Right Upper Lobe

The heart and mediastinal structures are shifted toward the right. On fluoroscopy, the heart shifted more toward the right on inspiration than on expiration. On the bronchogram, at the level of the carina, the tiny blind orifice of the right upper lobe bronchus is visible. What appears to be right upper lobe actually represents upward displacement of the middle lobe, since the normal upper lobe bronchial take-off is always at the level of the carina.

Lobar agenesis is an extremely rare congenital pulmonary anomaly, even more rare than agenesis of an entire lung. It may be associated with a variety of other congenital anomalies. The developmental error presumably occurs at the 5 to 7 mm. embryo stage at which time the two right lateral bronchial buds normally appear. Roentgenologically, there may be a decrease in aeration of the involved lung field, displacement of the hilum toward the affected lobe, and compensatory emphysema of the adjacent normal lobes. The heart and mediastinum are shifted toward the side of the lesion, more so on inspiration, and the diaphragm may be elevated. Herniation of the normal lung across the anterior mediastinum may occur. Vascular markings may be decreased on the side of the agenesis. Bronchography is diagnostic, as in the present case. Bronchial rearrangement may make it difficult to recognize the absent or rudimentary bronchus.

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Case Report Section

Interventricular Septal Rupture as a Result of Myocardial Infarction with Survival for 18 Months

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Rupture of the heart has usually been considered to be immediately fatal. Numerous case studies refute that impression. Hymen[1] reported an instance of a young Negro who was able to run nearly a quarter of a mile with a knife blade sticking through his chest and piercing his left ventricle. Other observers have reported similar experiences. Vaughan,[2] Constantine,[3] and Hesse[4] have collected many such cases from the literature. With present surgical skill, the heart has lent itself to even more dramatic recoveries.

In this traumatic group, the uninjured portion of muscle is usually normal and has an abundant reserve. Rupture as result of cardiovascular pathology does not offer the same hopefulness. The entire coronary tree is likely to be diseased with resulting diffuse myocardial damage. The reserve of the heart is therefore at a minimum so that surgery, even though immediate and heroic, is unable to overcome this absence of support.

This lack of surgical aid does not mean such perforations need invariably be fatal. With the employment of anticoagulants, improved hospital facilities, a broader understanding of the mechanism and control of heart failure, and measures to control shock, medical management can salvage a number of cases which ordinarly would be considered hopeless.

Rupture of the heart following an infarction is not a rarity. Beresford and Earl[5] reported a high incidence of such ruptures in mentally defective patients. They ascribe such occurrences to the fact that such patients are less aware of pain and therefore exert themselves unduly without proper restrictions. The ruptures were most likely to occur between the third and 12th day when the area of infarction was softest.

Most of such ruptures are through the wall into the pericardium. Perforations of the septum are more rare. The septum has a better collateral circulation and is therefore less susceptible to complete occlusion. When such a perforation does occur, it indicates extensive coronary disease.[6, 7] Gross[8] in his studies of coronary arteries by means of injection, noted the rich anastomosis of arterial supply in this region. With a septal perforation, branches of both the anterior and posterior descending coronary arteries are likely to be involved. Furthermore, the relative freedom of the septum from marked changes in pressures applied to its sides, tends to preserve its integrity.

Recognition ante mortem is becoming increasingly more frequent. The literature contains many such reports.

Latham[9] in his "Lectures on the Heart," published in 1845, first reported the rupture of an infarcted septum. Sager,[6] in 1934, compiled a list of 18 known cases; Diaz, Rivera, and Miller,[10] in 1946, reviewed 37 cases. Of these, only seven had been diagnosed ante mortem.

Survival after such an insult is still a rarity. In reports prior to 1934, all patients died within 10 days after the perforation. In 1936, Gross and Schwartz[11] described a septal defect occurring in a patient who died 14 months later. Wood,[12] in 1942, reported a case who lived almost five years. A number of other clinicians have reported their experiences with this condition.[16-21]

I should like to report such a perforation of the septum in a 54 year old man who survived for 18 months.

The diagnosis in my patient was verified by post-mortem examination. The heart is in the pathology museum at the University of Iowa. At autopsy, the heart was markedly enlarged—about three times normal size. The pericardial sac was adherent over the tip and over a portion of the left ventricle. At the apex, there was a large aneurysmal sac about the size of a golf ball. Its wall had thinned out and was practically the thickness of the pericardial sac. On opening the heart, the right ventricle showed considerable hypertrophy. On its inner surface where the blood current must have struck the wall after passing through the perforation, there were several elevated yellowish gray plaques. The walls of both auricles were also thickened and hypertrophied. The tricuspid and mitral valves were thickened but otherwise intact. The aortic and

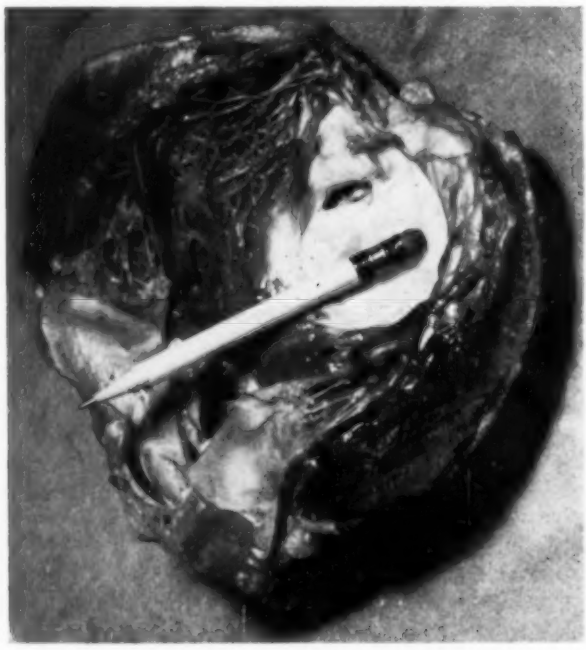

FIGURE 1: Heart showing aneurysmal sac and perforation of the septum.

pulmonary valves appeared normal. The chordae tendinae and papillary muscles were markedly hypertrophied. The aneurysmal sac included the septum and near the tip, there was a perforation measuring 1½ centimeters long. There was a free connection between the right and left ventricles. (Figure 1)

With this degree of damage, it seems almost impossible that such a heart could have supported life. That it did, is another example of the tremendous reserve and recuperative ability of the cardiac muscle. It again emphasizes the adage that where there is life, there is hope.

The clinical course of this patient is instructive in demonstrating the capabilities of medical management even in the face of the most adverse circumstances.

This patient had been a known hypertensive for over five years. In 1949, he was stricken with a cerebral hemorrhage from which he recovered with no apparent sequelae. He continued, however, to carry blood pressure elevations ranging from 260/130 to 220/120. The heart showed moderate left ventricular enlargement. The fundi showed Grade II sclerotic changes. Headaches were a frequent complaint. Nevertheless, he was very active in many business, community and social undertakings. Although warned that such conduct was contraindicated, he refused to heed all advice. Recommendations in my office, at the Mayo Clinic, and elsewhere, were consistently ignored. Some understanding of his background clarifies this attitude. This man was very small in stature, 5′2″, and was keenly aware of being so short; he was an immigrant who started in this country with nothing at all, but worked himself up to a position of prominence solely through determination and dogged perseverance. This deep rooted need for over-compensation could not yield to any slowdown.

For two days prior to hospitalization, he admitted experiencing shortness of breath, fatigability and "chest heaviness." His usual strenuous program was, however, continued until he collapsed in his office. When seen shortly thereafter, he was ashen in color and complained of unbearable substernal pain. Aside from shock, physical examination disclosed no significant abnormality. The heart sounds were normal—there were no murmurs or friction rubs. His blood pressure was 180/100. A presumptive diagnosis of coronary occlusion was made. A hypo of 75 mg. of Demerol was given and hospitalization immediately accomplished per ambulance. Within minutes, he had the benefit of oxygen therapy, Heparin and sufficient medication to control all pain. A tachycardia of 120 continued, but his pulse was regular and of good quality. The electrocardiogram showed extensive S-T changes of a massive infarction. (Figure 2 ECG). The WBC was 13,800; the sedimentation index by Cutler method 17 mm/hr. Although apprehensive, his condition remained satisfactory, but he had considerably more pain than is usually noted, and required frequent large doses of opiates.

Seventy-two hours after admission, he suddenly went into profound shock. Deep cyanosis developed. His pulse became thready, irregular and at times not palpable. The blood pressure dropped to 105/70 and shortly thereafter to 70/60. On auscultation, a harsh loud systolic mur-

mur was heard over the entire precordium. A thrill was palpable to the left of the sternum in the fifth interspace. The heart dilated so that it filled the entire thoracic cage. Blood tinged froth filled his throat and required constant suction. The ECG showed an altogether different picture of right heart strain.

Several possibilities had to be considered. The essential diagnostic features were those of a recent coronary occlusion plus physical findings seen in a congenital patency of the interventricular septum—namely a loud systolic murmur over the entire precordium with the PMI in the fifth left interspace and associated with an intense purring thrill to the left of the sternum. These constitute the classical signs of a congenital septal defect as described by Roger.[13] The additional finding of right heart failure, added further support to a diagnosis of an interventricular septal rupture. The time factor, three days after the occlusion likewise made the presumption more plausible.

In the differential diagnosis, one could immediately exclude coronary occlusion in a patient with a previous septal defect. This man had been examined many times previously to his last illness with no findings of such a defect. Furthermore, patients with such defects seldom live to an age that is subject to heart attacks.

A rupture of the papillary chorda tendinae muscle in the left ventricle could conceivably produce similar murmurs. Voigt[14] reported nine such

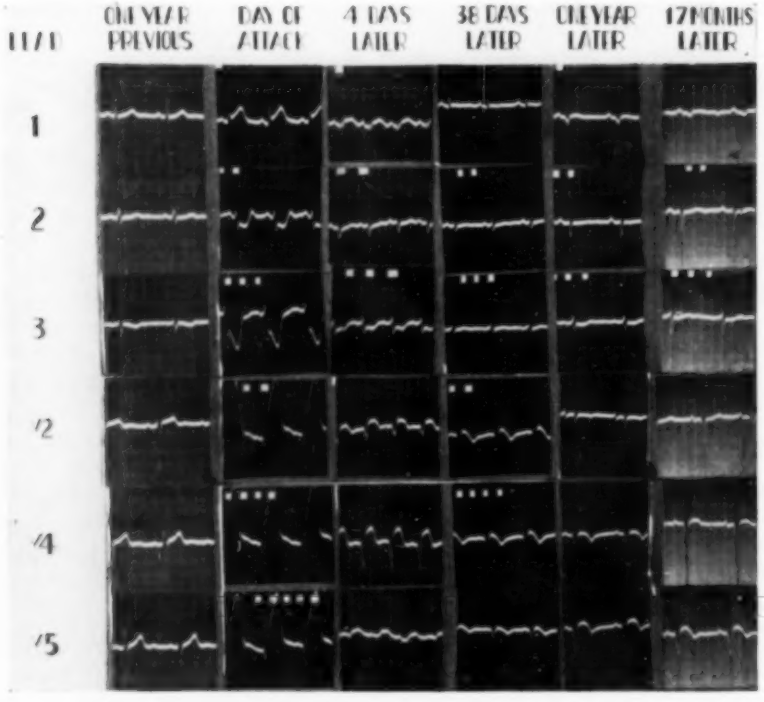

FIGURE 2: Electrocardiograms taken before and during various stages of his infarction and course thereafter.

cases. In four, there were no striking auscultory findings. In the others, the murmur was more often diastolic. The ECG findings in these pointed more to left than to right failure.

A relative tricuspid insufficiency as a result of weakness of the right ventricle had also to be considered in explaining the systolic murmur. Here the murmur is loudest over the xyphoid and a thrill is not present.

The rather characteristic findings together with a reasonable exclusion of other possibilities, warranted a diagnosis of a post infarction rupture of the interventricular septum. As I previously stated, this diagnosis was later confirmed.

Case reports of the clinical course of patients who have survived such an insult do not report such extensive involvement. Those who did survive any length of time, at best, lived a life of chronic heart failure. Reports indicated the left ventricular failure, after the acute stage, was not marked. Right heart failure was, however, progressive and unyielding.

The mechanism of such failure is explained by three influences.

1. Permanent injury to the wall of the left ventricle.
2. Fibrous replacement of the septal myocardium which permits a bulging convexity into the right ventricular cavity. This excessive intrusion causes embarrassment. This condition constitutes the so-called Bernheim syndrome.[15, 22]
3. The pressure in the left ventricle being greater, patency of the septum permits the leak of blood from left to right. Although this may somewhat relieve the strain on the damaged left chamber, it places an overwhelming burden on the thinner walled right ventricle. The heart reverts to a condition approaching that of Cor Triloculare. Excessive blood is sent to the lungs from both chambers of the heart and accumulates there at the expense of the systemic circulation. This results in pulmonary congestion and systemic inadequacy. One sees a marked disproportion between the force of the heart action and the strength of the pulse. Likewise, the arterial blood pressure, which is indicative of left ventricular function, is consequently low.

I frankly felt that the prognosis in my patient was hopeless. For days following his perforation, coma due to cerebral anoxia and uremia resulted in only short periods of consciousness. In rapid succession, every conceivable complication occurred. Auricular fibrillation responded to Quinidine; broncho pneumonia resolved with Penicillin and Dihydrostreptomycin; recurrent bilateral pleural and peritoneal effusions required repeated paracentesis of large quantities of straw colored transudate; anuria—at one time complete for three days, was overcome by intravenous fluids, digitalis, diuretics and repeated Wyamine Sulphate injections when blood pressure readings were unobtainable. For twelve weeks, he remained a medical enigma—every minute appeared to be his last. In this period, his precarious existence demanded constant attention. Special nurses never left his room. Oxygen ran constantly. His prothrombin time was maintained between 30 and 40 seconds; nourishment, fluid and electrolyte requirements were provided by clysis. Every threat, and

they seemed unending, was immediately challenged, but success seemed to offer only a temporary respite from further difficulties.

As difficult as was his management when he was in coma, it became even more complex when he regained consciousness. Alternately, he voiced optimism about resuming a full schedule of activity, only to be followed by the complaint that recovery was impossible and that he wished he were dead. He refused salt restriction and rebelled against salt substitutes. All necessary restrictions were waved aside far ahead of his capabilities. Had I not known this man intimately, I would have felt that his conduct was secondary to brain damage. His attitude and reactions were not, however, much different from his normal drive before his illness.

After 12 weeks in a state of hibernation, gradual recovery ensued. He became able to take small amounts of nourishment, normal renal function resumed, and he tolerated short periods out of oxygen. The blood pressure rose to 105/70 and remained there. The heart, however, continued to fill the entire chest. Moist rales were audible over both lung bases, the liver was soft and enlarged 3x below costal margin and the characteristic heart murmur remained unchanged.

Removing him from oxygen was a real problem. When he was alert to his environment, a tent gave him a sense of claustrophobia, prolonged catheter insertion was irritating and he kept pulling it out, cannulas tickled his nose, and when oxygen was removed, he became deeply cyanotic. By gradually increasing his periods out of oxygen, after several weeks, he was able to tolerate this absence for several hours at a time. Shortly thereafter he could dangle for brief periods.

Fourteen weeks after admission, he returned to his home—a cardiac invalid—Grade IV activity was maintained only through benefit of digitalis, quinidine, tromexen, diuretics and a salt free diet. The latter annoyed him particularly—salt substitutes were rejected and every opportunity to eat improper foods was readily seized.

Six weeks later he developed hepatitis with severe jaundice—probably a result of contamination during his numerous veno-punctures in the hospital. The serum bilirubin reached 33.5 and the icterus index 190. His previous routine was continued with the exception of the anticoagulants which were of course no longer needed—thereafter the prothrombin time maintained itself at almost the previous levels. Whereas previously he insisted upon eating excessive amounts, he now refused any nourishment.

This hurdle was likewise overcome. Gradual resolution of the hepatitis occurred. Four months after its onset, he became ambulatory around the house; a month later, he was able to venture outside for short periods. Soon thereafter, he traveled to Florida for the winter. Close medical and nursing supervision could not, however, restrict his activities. He seemed to delight in defying advice. Marital relationship loomed as a major challenge. He insisted even though it caused panic to his wife and utter exhaustion to him. He even attended a night club in Miami Beach and stayed to see the late show.

Although defying all the rules of expectation, he did survive to return home. He was beautifully tanned, and to all outward appearances looked a picture of health.

Imbued with all the wealth he saw in Florida, he was more than ever determined to add to his worldly means. More and more deals had to be accomplished—and at a faster pace. Although his will was indomitable, his heart was rebellious. He was more short of breath, and was constantly tired. His repetitious conversation bespoke the cortical changes of prolonged anoxia.

With utter defiance, he continued his catapult to self destruction. After a hectic day going to his office, to his bank, to his barber, after purchasing a car and driving it home in the rain, he suddenly slumped in his chair and was gone. When I arrived, the western thriller on the television set he was watching, continued to blare out, noisily symbolic to the very end of the intense activity he so constantly craved.

This case taught me never to tell a family that the prognosis is hopeless—that a patient will die within a given period of time. Certain factors beyond a doctors' skill and experience control that ultimate decision. This case was also instructive as well as self satisfying in its diagnosis, and in the management of almost all aspects of cardiac complications. The literature has been reviewed and salient clinical and pathological features have been outlined.

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Multiple Foci of Tuberculosis Including Subcutaneous Abscesses from Hematogenous Dissemination

JOHN A. HARBINSON, M.D.

Honolulu, Hawaii

This report concerns a patient with moderately advanced pulmonary tuberculosis who subsequently developed multiple foci from hematogenous dissemination. During the early period of hospitalization, his condition was considered hopeless on many occasions. The development of subcutaneous tuberculous abscesses, was a striking feature. The slow but dramatic recovery is related in this case report.

Case Report

A 38 year old Filipino janitor was admitted to Wahiawa Hospital, Oahu, on May 10, 1945 with a diagnosis of pulmonary tuberculosis, 2 C, active (See Fig. 1). In late 1944, he began to feel poorly. In May 1945, he noticed onset of productive cough and weakness.

He was then transferred to Leahi Hospital on February 25, 1946 with moderately advanced pulmonary tuberculosis and a number of separate tuberculous lesions as depicted in Fig. 2. X-ray films of the left knee joint on admission showed considerable periarticular thickening, soft tissue swelling and evidence of increased fluid in the knee joint.

In October 1946, massive doses of peniciilin were given to control the secondary infection of the "soupy" left knee and the subcutaneous abscesses. In November 1946, atabrine instillations of the abscesses on the left forearm were performed following aspiration, and they were apparently healed by the end of December 1946. On August 8, 1946, 4 to 5 cc. of 1 per cent atabrine were instilled in the abscesses on both legs, back and neck following aspiration of pus. By the end of September 1946, these showed evidence of healing or of having healed after one or more instillations of atabrine.

Fluid aspirated from some of these subcutaneous abscesses was positive for acid fast bacilli either on culture and/or guinea pig inoculation one or more times during 1946. Atabrine instillations were given because of their alleged bacteriostatic effect in vitro.

From Leahi Hospital, Honolulu, Hawaii.

In July 1947, he developed extension of the process in the left leg to the thigh and pelvis, progressive pitting edema of the left lower extremity and abdomen extending up over the lower chest which was less marked on the right side and believed due to associated caval thrombophlebitis. All the other subcutaneous abscesses simultaneously began to drain. The edema became most marked in December 1947 and, at this time, his condition was considered hopeless. Amputation of the left leg was performed December 12, 1947 (Fig. 3). Following this, his temperature began to decrease and his clinical condition improved tremendously. Histological examination of sections taken from the amputated left lower extremity by Dr. I. L. Tilden, pathologist at the Straub Clinic and consultant pathologist at Leahi Hospital, showed an extensive tuberculous process beneath the epidermis characterized by caseation, necrosis, and epithelioid and giant cell formation.

Streptomycin, 1 Gm. daily, was given between December 1947 and April 1948. Promizole, 2 Gm. daily, was given between April 24 and August 2, 1948. By July 1948, the only subcutaneous lesions not healed were in the left axilla and over the posterior aspect of the right shoulder joint. All tuberculous subcutaneous abscesses and sinuses were healed by the end of 1949 and have so remained.

Streptomycin, 1 gram daily, was recommenced January 1951 and continued through April 1951. Thereafter, PAS alone, up to 12 grams daily, was given until June 1951. In December 1952, streptomycin, 1 gram every three days, was recommenced and continued until September 1954. INH was commenced February 1953 and has been continued to the present time; he now tolerates 300 mgm. daily.

Sputum studies from February 1946 through 1948 were occasionally positive on concentration and culture. Sputum concentrates from May 1949 through June 1950 showed many acid fast bacilli. Thereafter, sputum cultures to 1951 were only occasionally positive. He again had positive sputum cultures during February and March 1953. The last positive was reported April 20, 1953, one colony. These findings coincided with extension of disease in both lung fields. Since that time, all sputum studies have been negative, both on concentration and culture. The pulmonary tuberculosis has been inactive since January 1954 (Fig. 4).

In April 1948, he developed clinical and laboratory signs of cholecystitis, and gallbladder series showed a nonfunctioning gallbladder. In August 1948, he complained of vague abdominal pain. Hepatosplenomegaly with tenderness was present and it was thought he had portal hypertension. However, barium swallow failed to reveal esophageal varices. During both of these episodes, he was treated conservatively, using supportive measures.

By the end of 1948, he noted pain in the lower lumbar region. X-ray films at this

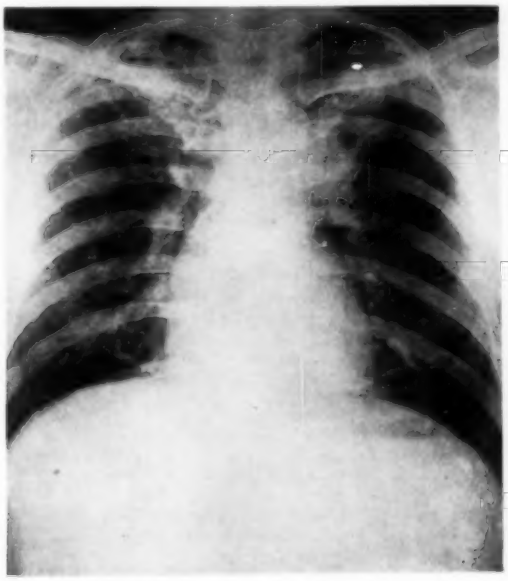

FIGURE 1: Admission X-ray showing fibrocaseous lesions involving both upper lung fields, May 19, 1945.

time showed a suggestive area of destruction along the inferior border of the 12th dorsal vertebra, some narrowing of the disc space between D-12 and L-1, and a psoas abscess on the left (Fig. 5, a and b). The spinal disease improved satisfactorily on bed rest without surgical intervention. By June 1952, it was considered arrested (Fig. 6, a and b) and, at present, there is no evidence of active disease. The only residual x-ray finding is a slightly narrowed disc space between the 12th thoracic and first lumbar vertebrae.

Appendectomy for acute suppurative appendicitis was performed February 1, 1949. Histological examination showed an acute suppurative inflammatory process manifested by partial destruction of the mucosa and widespread leukocytic infiltration in the wall. Inflammatory exudate was present in the lumen and the predominating infiltrating cells were polymorphs. However, in one section, a small epithelioid tubercle was present with a Langhans' giant cell, suggesting involvement by tuberculosis.

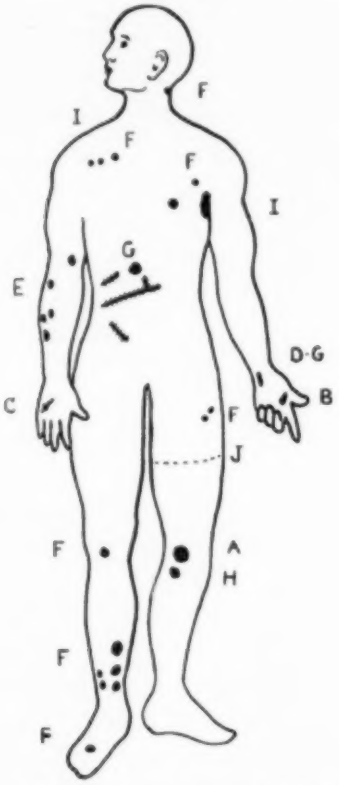

FIGURE 2: Line diagram of body showing multiple sites of tuberculous subcutaneous abscesses (27): (a) October 1945—Onset of soft swelling over medial condylar area, left tibia, with periarticular thickening and effusion of left knee joint. (b) January 1946—Onset of soft swelling between left thumb and index finger; March 1946—Incision and drainage, AFB positive (culture and guinea pig); January 1947—Still draining. (c) February 1946—Draining sinus, right palm, on admission; December 1949—Small swelling; April 1950—Tenolysis and excision, sinus tract and scar. (d) March 19, 1947—Onset. (e) March 30, 1946—Onset of fluctuant masses; July 1946—Incision and drainage. (f) August 1946—Onset of abscesses, both legs, back and neck; June 1947—Abscesses, anterior upper aspect, left thigh, still draining. (g) October 1946—Onset, abscesses right anterior costal area and anterior aspect, left wrist. (h) April 1947—Another fluctuant mass developed over medial aspect, left knee joint. (i) July 1948—Only subcutaneous abscesses not healed were in left axilla and over the posterior aspect, right shoulder joint. (j) July 1947—Process in left leg extended into thigh and pelvis with progressive pitting edema, believed due to associated caval thrombophlebitis; December 12, 1947—Amputation, left leg, followed by marked improvement.

FIGURE 3

FIGURE 4

Figure 3: Lateral view of amputated left lower extremity showing markedly swollen joint. All bony elements of knee joint show moth-eaten appearance, December 12, 1947.—*Figure 4:* X-ray, January 4, 1956. Serial films since August 1953 are similar to above.

FIGURE 5A

FIGURE 5B

FIGURE 5: December 2, 1948, spine films.—*Figure 5A:* Left psoas abscess.—*Figure 5B:* Suggestive destruction, inferior border, D-12. Narrow disc space, D-12—L-1.

Because of pain in the left stump, revision of the amputation was performed October 18, 1949 when the scar was excised and a neuroma removed.

In August 1950, he developed symptoms and signs of obstructive jaundice. Exploratory laparotomy was done at which time the omentum was found to be wrapped around the gallbladder area and adjacent surface of the liver. Caseous deposits were noted throughout the liver as were tumorlike masses about the gallbladder and common duct (Fig. 7, a and b). Exploration only was done. On November 2, 1952, he had recurrence of right upper quadrant abdominal pain and jaundice. Further operation was performed December 26, 1952 when cholecystectomy and choledochojejunostomy were done. The common duct was explored and two stones removed. Histological examination of the gallbladder showed severe chronic cholecystitis manifested by marked fibrous thickening of the wall and focal and diffuse lymphocytic infiltration. The mucosa was relatively well preserved although dense lymphocytic infiltration was present between the epithelial elements. Histologically, it was not suggestive of a tuberculous process. Histological examination of a liver biopsy showed old hyalinized tuberculous nodules.

In June 1955, he was provided with a left lower extremity prosthesis which he has since been using.

Because of persistence of microscopic hematuria since April 6, 1955, cystoscopic and retrograde pyelography were carried out December 28, 1955. The findings were granulations in the posterior urethra including the prostatic portion and that anterior to the verumontanum, and a cyst on the verumontanum which was electrocoagulated. Studies for acid fast bacilli and routine pathogens have always been negative. The NPN, BUN and creatinine have been within normal limits and the Fishberg concentration test showed maximum specific gravity of 1.021.

A Congo red test performed on October 14, 1955 showed 17 per cent disappearance of dye in one hour. Bromsulphalein test on December 29, 1955 showed 21 per cent retention of dye in 30 minutes. Serum proteins, A/G ratio 4.4/2.9 = 1.5:1 and cephalin-cholesterol flocculation test showed 4 plus at 24 and 48 hours on the same day.

The last evidence of an active focus was in February 1953 when he had an exacerbation of the pulmonary disease. He was ambulated June 29, 1956.

Now, all foci of tuberculosis are considered inactive and efforts are being made to return him to a useful life.

Discussion

The medical literature has been thoroughly scrutinized for subcutaneous tuberculous abscesses and the only articles available[1] describe tuberculosis of the subcutaneous tissues in cattle and no information on the human form is available. It is described as

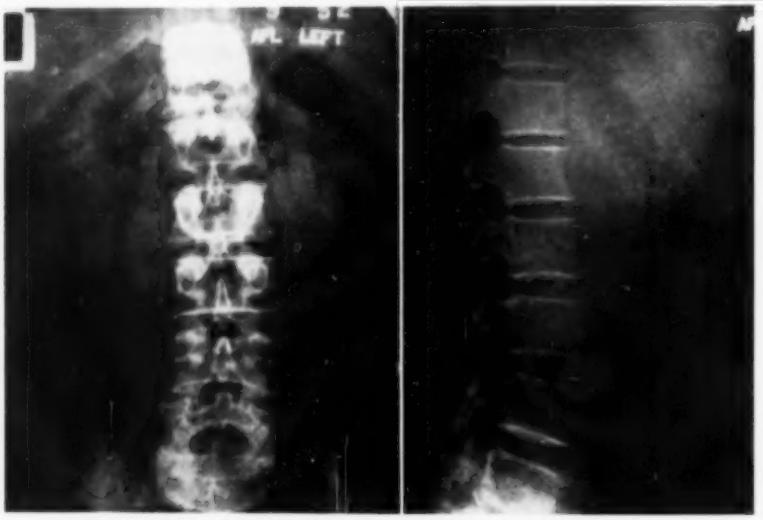

FIGURE 6A FIGURE 6B

FIGURE 6: June 9, 1952, spine films.—*Figure 6A:* Disappearance of psoas abscess.—*Figure 6B:* Some narrowing of disc space, D-12—L-1.

FIGURE 7A FIGURE 7B

Figure 7, A and B: Abdominal film showing calcification in the liver.

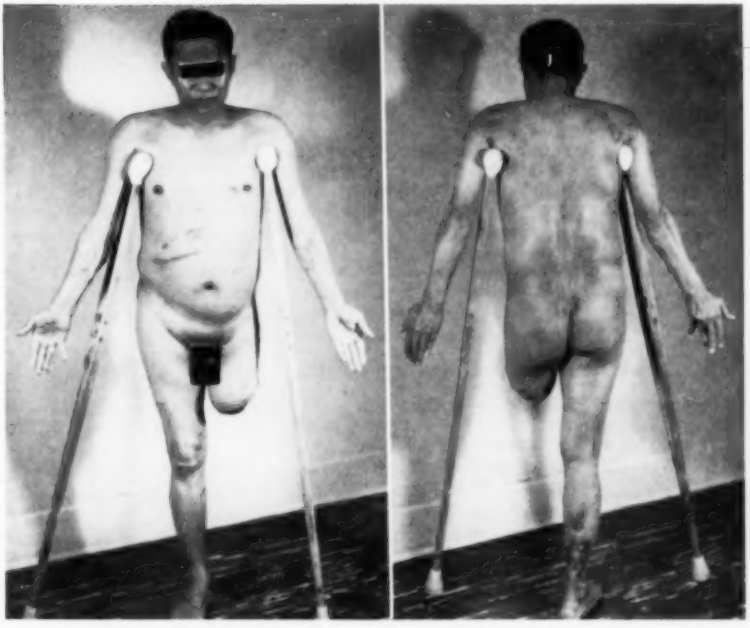

FIGURE 8A FIGURE 8B

Figure 8, A and B: The patient today.

occurring in the subcutaneous tissues and in the fascial places between muscles in chains following the lymphatics.

The whole subject of tuberculous subcutaneous abscesses is no doubt related to the subject of tissue resistance.[8] Churchill postulates biochemical factors which may influence the fate of tuberculosis in tissues. J. G. Hirsch of the Rockefeller Institute for Medical Research, New York, claims that other mechanisms are involved besides exposure and anatomical features. Birkhauser mentions that the kidney of the guinea pig possesses a marked resistance to tubercle bacilli.

The inhibitory activity of drugs on tubercle bacilli is, in many instances, associated with molecules having prominent basic (amino) radicals in their structure. Streptomycin and isonicotinic acid hydrazide are examples among the chemotherapeutic compounds. Spermine and spermidine which occur in animal tissues, and pancreatic desoxyribonuclease and testicular hyaluronidase manifest antimycobacterial activity provided Tween 80 is in the environment (Fletcher et al., 1953). Basic peptides, binding or otherwise rendering sulfate ion unavailable to bacteria (Hirsch 1954), deprive the micro-organism of a source of sulfur essential for their growth. The state in which peptides exist in intact tissue is unknown. They may be released as the result of an autolytic process accompanying inflammation or necrosis.

Findings of this sort lend support to the general thesis of the effect of the local chemical environment on the fate of tubercle bacilli. Extensive early bacterial multiplication results in caseous necrosis; the bacilli can no longer survive, probably because of oxygen deficiency, CO_2 excess, accumulation of organic acids and release of lysozyme, etc. (Canetti).

Perhaps some of the immunity associated with sensitization exerts its effects via changes in the local biochemical environment. Two metabolic alterations associated with diabetes mellitus, viz. decreased lactate production and accumulation of ketone bodies, tend to render conditions in the tissues of the diabetic individual unusually favorable for the survival and multiplication of tubercle bacilli. Martin and co-workers, in 1954, have shown cortisone brings about a reduction in lactic acid production by leukocytes in vitro.

According to Rich,[3] progressive destructive lesions in humans are rare in skeletal muscle, thyroid, pancreas, heart, liver, spleen, ovary and testis. The liver has a high degree of organic resistance to tuberculosis. It may be attributed to the attenuating effect of the bile, according to Lichtman:[4] It is unusual that this patient displayed no evidence of tuberculous involvement of the gallbladder, the common duct or duodenum while, at the same time, showing definite evidence of disease in the liver and spleen. The infrequency of tuberculous cholecystitis associated with tuberculosis of the liver is due to increased resistance of the gallbladder mucosa and the adverse effect of bile according to Schwartz, Gilman and Settle.[10] Sergent[11] suggests that the fat-splitting and dissolving properties of bile and pancreatic juices might possibly alter the fatty coat of the tubercle bacillus.

Cleve, Gibson and Webb[5] describe four cases of atypical tuberculosis of the liver associated with jaundice occurring in Filipino men in which they were able to demonstrate tubercle bacilli and, histologically, the lesions were compatible with tuberculosis. It was not confirmed by culture. In these patients, the most common manifestations were fever, chills, hepatosplenomegaly, abdominal distress with mild to moderate jaundice. All responded well to streptomycin and follow-up was satisfactory.

Melville[16] described a case of tuberculosis of the liver diagnosed at laparotomy. The patient also developed tuberculous arthritis of the left elbow joint proved by culture at a later date. There was no evidence of miliary tuberculosis and good response was obtained from daily streptomycin over a three-month period.

With the advent of antituberculosis drugs, the statement, "A fatal termination may be expected in tuberculosis of the liver," is no longer valid.

ADDENDUM

Since the writing of this case report, a 29-year-old Japanese man was admitted to Leahi Hospital August 9, 1956 for complete genitourinary re-evaluation in view of continued positive urine cultures for acid fast bacilli.

He had three previous admissions to Tripler Army Hospital.

1) April 1948 to September 1949, with right tuberculous pleural effusion and pericarditis. Urine studies were negative for acid fast bacilli.

2) December 1949 to May 1954, because of fever, leukopenia and splenomegaly. Splenectomy was performed. Miliary tubercles were found in the liver and spleen. Sputum was positive for acid fast bacilli. He was treated with streptomycin and PAS. In June 1950, an abscess of the left ankle developed and persisted six months. Streptomycin and PAS were stopped in July and September 1950, respectively. In July 1951, he developed a tuberculous abscess of the penis which healed after two months of streptomycin and Tibione. In September 1951, a tuberculous abscess of the left deltoid area developed and healed after several months. In March 1952, streptomycin and Tibione were stopped. In April 1952, he again became febrile.

Dihydrostreptomycin produced no response. Isonicotinic acid hydrazide was added June 1952. In April 1953, a minimal left pleural effusion was present. In March 1953, urine cultures were reported positive for acid fast bacilli and have continued so intermittently.

3) Because of this, he was readmitted to Tripler Army Hospital in May 1955 for two weeks. Dihydrostreptomycin was stopped February 14, 1956 and he is presently receiving calcium PAS and INH.

He was admitted to Leahi Hospital August 9, 1956 to September 5, 1956. Bladder urine specimen was positive for acid fast bacilli on guinea pig inoculation. During hospitalization, diagnoses were established of tuberculosis of the right kidney, right testis and epididymis, activity undetermined but probably active.

This patient, therefore, had a past history of right and left pleural effusion, pericarditis, miliary tuberculosis of the liver and spleen, subcutaneous tuberculous abscesses; these lesions are presently inactive.

Acknowledgment: The author wishes to thank Dr. H. H. Walker, Medical Director of Leahi Hospital, and Dr. P. W. Gebauer, thoracic surgeon at Leahi Hospital for their invaluable assistance in the preparation of this paper.

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HISTORY OF THE COLLEGE

Dr. J. Arthur Myers, Minneapolis, is to be congratulated on the splendid twenty-five year *History of the College* which he recently completed and which is now in the process of publication. The College history is being published in commemoration of our Silver Anniversary year and we are indebted to Dr. Myers, the Editor-in-Chief of *Diseases of the Chest*, for assuming the tremendous task of recording all of the activities of the College since its inception. The history comprises 136 pages and is profusely illustrated. Mr. Allen Carr, a prominent Chicago artist, designed the cover, a beautiful drawing of the College building.

A complimentary copy of the history will be mailed to every College member throughout the world in the near future. We are sure this chronicle of events and achievements during the twenty-five year history of the American College of Chest Physicians will prove interesting to each member and will become a valuable addition to his library.

Donald R. McKay, *President*

SILVER ANNIVERSARY MEETING

The 25th Annual Meeting of the American College of Chest Physicians will be held at the Ambassador Hotel, Atlantic City, June 3-7, just preceding the 108th meeting of the American Medical Association, June 8-12. The complete program for the College meeting appeared in the April issue of *Diseases of the Chest*. Additional copies of the program may be obtained by writing to the Executive Offices of the College, 112 East Chestnut Street, Chicago 11, Illinois.

Advance registration for the Silver Anniversary meeting indicates that there will be a record attendance. It is suggested that hotel reservations be requested at once, as accommodations will become scarce in the near future. Members who plan to attend the meeting may write directly to the Ambassador Hotel for their reservations, giving arrival and departure dates.

The extremely interesting and extensive scientific program, plus many special functions planned for this session will make a visit to Atlantic City worthwhile and enjoyable. It is hoped that all members in the United States and other countries will make an effort to attend.

College Chapter News

ARGENTINE CHAPTER

The annual meeting of the Argentine Chapter was held in Santa Fe, November 22. The scientific program was devoted to a discussion of "Home Treatment of Tuberculosis" and "Surgical Treatment of Pleural Emphysema." Dr. Alfredo Howard, Buenos Aires, spoke on the first subject, and Drs. Antonio Juaneda and Julio Escarguel Malbran of Cordoba, led the discussion on emphysema. After the scientific session, the following officers were elected:

President	Isaac F. Wolaj, Cordoba
Vice President	Carlos W. Grobli, Buenos Aires
Secretary-Treasurer	Mario Gomez Casco, Cordoba

JAPAN CHAPTER

The annual meeting of the Japan Chapter took place in Tokyo on February 13, at which the following program was presented:

"Hamman-Rich Syndrome"
Kingo Shinoi, Tokyo

"Cleaned-out Healing of Pulmonary Tuberculosis"
Taizo Kumagai, Sendai

"Studies on Heredity of Tubercle Bacilli and Viruses"
Masanaka Terada, Tokyo

At the close of the scientific session, the following chapter officers were elected:

President	Imasato Donomae, Osaka
Vice President	Yasuyuki Kano, Tokyo
Secretary-Treasurer	Jun Nagasawa, Tokyo

HONG KONG AND CHINA CHAPTER

The Hong Kong and China Chapter met on January 27 at the Hong Kong Sanatorium and Hospital. Dr. A. S. Moodie, Government Senior Specialist in Tuberculosis, presented a paper on "The Official Attack on Tuberculosis in Hong Kong," which was followed by open discussion. Dr. S. D. Sturton, chapter president, presented x-ray films for discussion.

WEST INDIA CHAPTER

The inaugural meeting of the West India Chapter was held in Bombay on December 27. In attendance were: (seated, left to right) Dr. J. K. Lashkari, Secretary-treasurer; Mrs. B. R. Billimoria, Dr. B. R. Billimoria, Governor of the College for West India; Dr. N. N. Kailas, Minister of Health, Government of India; Dr. R. J. Vakil, President, West India Chapter; Mrs. J. R. Vakil, Mrs. N. Kailas. (Standing, left to right): Dr. P. E. Billimoria, Mrs. S. N. Chak, Lt. Col. S. N. Chak, Dr. Pujari, Mrs. P. E. Billimoria, Dr. S. G. Advani, Dr. K. K. Datey, and Dr. V. M. Bahulkar, Vice-President of the chapter.

NEW CHAPTER OFFICERS

CALIFORNIA CHAPTER

President	Thomas B. Wiper, San Francisco
Vice President	Samuel J. Sills, Los Angeles
Secretary-Treasurer	John Mack Baker, Sacramento

INDIANA CHAPTER

President	Gerald M. Wohlfeld, New Albany
Vice President	Alfred D. Dennison, Jr., Indianapolis
Secretary-Treasurer	Donald F. MacLeod, West Lafayette (re-elected)

EAST INDIA CHAPTER

President	P. K. Chatterjee, Calcutta
1st Vice President	Karun Sankar Ray, Calcutta
2nd Vice President	Krishna K. Chaturvedi, Namku, District Ranchi
Secretary-Treasurer	Debnarayon Roy Choudhury, Calcutta

CALENDAR OF EVENTS

NATIONAL MEETINGS

Twenty-fifth Annual Meeting
Silver Anniversary, American College of Chest Physicians
Ambassador Hotel, Atlantic City, New Jersey
June 3-7, 1959

Homecoming Meeting
Silver Anniversary, American College of Chest Physicians
Albuquerque, New Mexico, October 14-17, 1959

CHAPTER MEETINGS

Mississippi Chapter, Biloxi, May 11
Illinois Chapter, Chicago, May 20

Book Reviews

THE SURGICAL MANAGEMENT OF PULMONARY TUBERCULOSIS. Edited by John Steele, M.D. With an introduction by Frederick A. Coller, M.D. Biographical sketch of John Alexander by Cameron Haight, M.D., 230 pp. with illustrations, plates, tables and charts. Springfield, Illinois: Charles C Thomas, 1957. $9.50 (Publication No. 1, the John Alexander Monograph Series.)

This book, covering all phases of the surgical treatment of pulmonary tuberculosis is the first of a monograph series dedicated to the memory of the late Dr. John Alexander—one of the truly great pioneers in the field of thoracic surgery. Thirteen of Dr. Alexander's former residents and two of his closest medical associates, all eminent authorities, have contributed to the text in a comprehensive manner.

The early pages present a biographical sketch of Dr. Alexander and his long career as surgeon and stimulating teacher. This is followed by 12 chapters, each dealing with a separate phase of the surgical treatment of pulmonary tuberculosis. The first chapter covers the evolution and historical aspects; photographs of many of the pioneers in this field of surgery are presented.

The next four chapters deal with pulmonary resection. The high morbidity and mortality rates in the pre-drug era are emphasized. The evolution of resection to its present status as the mainstay of surgical treatment is developed as the result of improvements in surgical and anesthetic techniques, but more particularly as the result of the effectiveness and protection of anti-microbial therapy. The increasing use of segmental resection is pointed out. The combined use of resection and collapse procedures is fully covered.

Conventional and extraperiosteal plombage thoracoplasty is dealt with in the next two chapters. Their place in the modern surgical program is presented as limited, but definite.

The surgical management of pleural tuberculosis is covered comprehensively in chapters eight and nine and cavernostomy in chapter 10. A short, but important chapter follows on the problem of surgical management of tuberculosis in the psychotic patient.

The last chapter is a comprehensive and well-written monograph on the chemotherapy of tuberculosis. The various drugs are discussed individually. Their relative effectiveness is analyzed. The problems of toxicity and bacterial resistance are clearly presented. The success and limitations of drug therapy are delineated. The correlation of drug therapy with surgical intervention is done especially well.

This monograph on the surgical treatment of pulmonary tuberculosis is comprehensive and authoritative. Its only shortcoming is that it contains little in the way of description and illustration of surgical techniques.

Norman J. Wilson, M.D.

ATLAS UND KURZGEFASSTES LEHRBUCH DER PHONOKARDIOGRAPHIE UND VERWANDTER UNTERSUCHUNGSMETHODEN. By K. Holldack, Professor Dr. med. and D. Wolf, Dr. med. $11.50. Pp. 179, with 160 illustrations. Georg Thieme Verlag, Verlagsbuchhandlung for Medizin und Naturwissenschaften, Herdweg 63, Stuttgart. 1958.

The atlas on phonocardiography is prepared with the usual elegance and care of German medical publications. This is often so beautifully done that one has a tendency to neglect the text. In this respect the present volume is indeed frequently disappointing, as clinical phonocardiography must be closely tied in, and is indeed a part of bedside diagnosis. The clinical diagnosis of heart disease, and particularly of auscultation, has been considerably refined during the last fifteen years through the conscientious application of new knowledge gained by physiologic diagnostic methods and by direct surgical inspection and quantitation. Much of this new information is missing or is inadequately represented and for this reason the book is not recommended without reservations.

On the other hand, the section dealing with physical and technical aspects of phonocardiography prepared by F. Schwarzer is outstanding and clearly presented. Throughout the volume phonocardiograms are reproduced using 3 or 4 band filters. This beautiful technique is certainly in advance of our own routine facilities. This book serves well to underscore our own technical deficiencies and should therefore be widely read in spite of some of its clinical shortcomings.

Hans H. Hecht, M.D.

BULLETIN . . . . . Washington, D. C.

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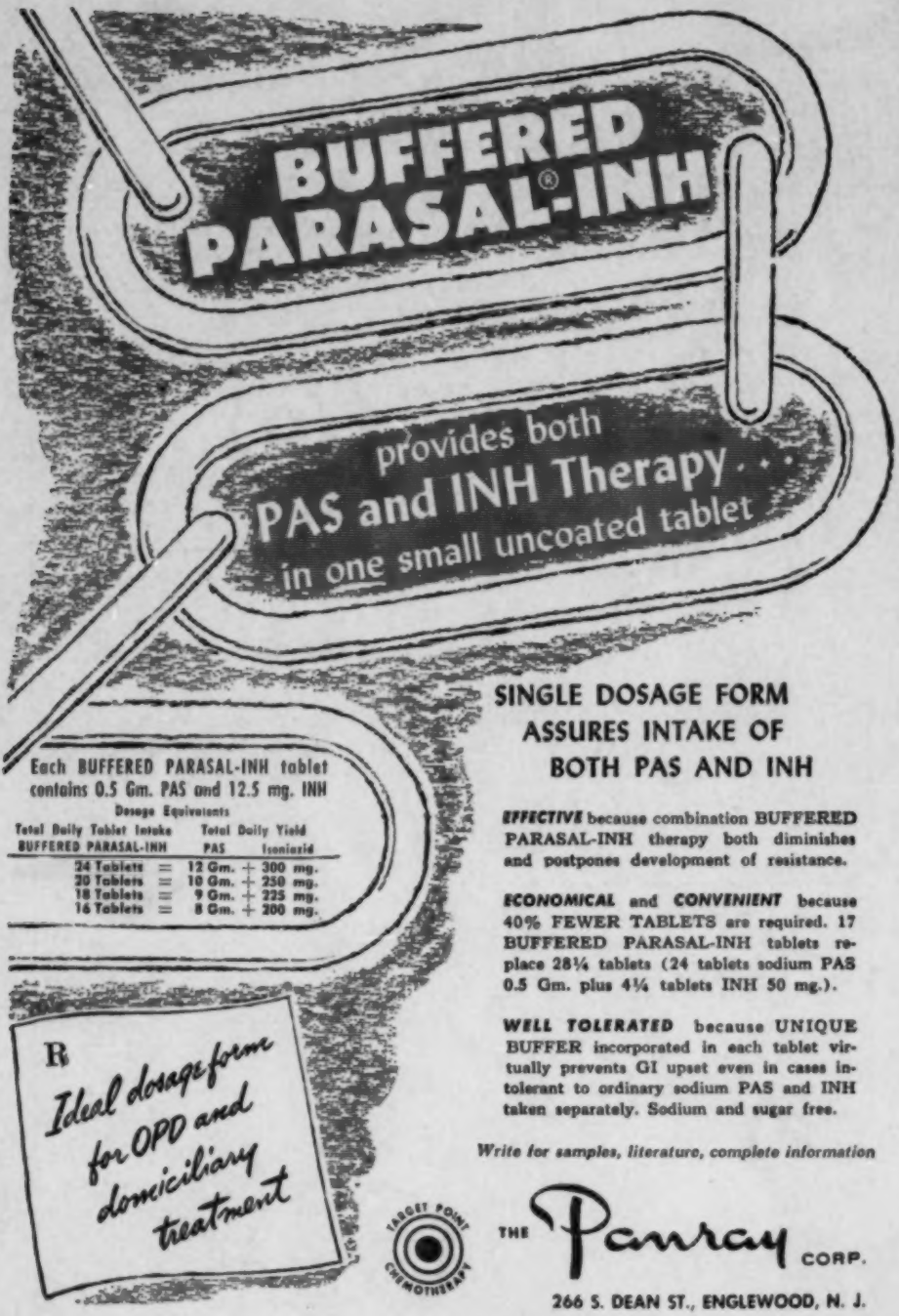

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